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13. Abstract ***(Maximum 200 Words)*** *(abstract should contain no proprietary or confidential information)*
Estrogen derivatives bind as ligands to the estrogen receptor initiating biological reactions, which can cause either initiation/progress or inhibition of tumor growth. Slight structural variations in these molecules can change their carcinostatic potentials from agonistic to inhibitory. The principle objective of this proposal is to relate known biological reactions to physical properties such as point charges of atoms and the electrostatic potential. We are obtaining information about these electronic properties of estrogen derivatives from experimental determination of their electron density using high quality single crystal X-ray crystallography. We derived electron density, electrostatic potential and related properties for six estrogen crystals. We have developed the methodology of the X-ray CCD data treatment and least-squares model refinement in order to extract maximum reliable information from the data. We found that the deformation electron density distributions of all hydroxyl oxygen atoms are near sp^3 in shape, their lone pair densities have been reliably located. These configurations as well as the electrostatic potentials around the oxygen atoms are very consistent in the different hydrogen bonding environments. The core estrogen structure is also very consistent between the derivatives. The significant differences are found at the activity-sensitive molecular parts.

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Introduction

The principal objective of this proposal is to obtain physico-chemical information on estrogen derivatives and correlate this knowledge to their known biological functionality. Slight chemical variation in these molecules can change the carcinostatic potentials from agonistic to inhibitory. Relating these biological reactions to physical properties such as point charges of atoms and the electrostatic potential is a logical first step in the intelligent design of therapeutical drugs. We are obtaining information about the electronic properties of estrogen derivatives from experimental determination of their electron density using high quality single crystal X-ray crystallography at low temperatures.

Body

Task 1. Preliminary Studies on a series of crystals of estrogen derivatives

- Development of crystallization methods for the derivatives not yet available as high quality single crystals

  Currently the best conditions found involve dissolving 17β-estradiol or 17α-estradiol in "wet" methanol. Allowing the solvent to evaporate as slowly as possible (~2-4 weeks) will yield charge density quality crystals. This results in the formation of different crystal systems (such as 17β-estradiol • ½ MeOH or 17β-estradiol • ⅔ MeOH • ⅓ H_2O).
  On the contrary, the best estriol crystals were obtained from acetonitrile, and the best estrone crystals - from ethanol: ethyl acetate system.

- Variable Temperature studies on each sample to define the appropriate temperature for the measurement

  Several crystals were taken to the synchrotron source at Argonne National Labs in order to obtain data below liquid nitrogen temperatures. These tests were unsuccessful as we encounter problems with crystal stability while cooling to liquid helium temperatures.

- Routine X-ray crystal structure determination on uncharacterized derivatives

  The manuscript on the new crystal structure of 1,3,5[10]-Estratriene-3,17β-diol Solvate: Estradiol 0.66(CH_3OH) 0.33(H_2O) has been prepared and submitted (**Appendix A**).

Task2. Electron density studies on the above mentioned estrogen analogues

- Electron density studies at nitrogen temperatures

  To develop a procedure, how to get fast (in several hours) high quality charge density data for estrogens, the estrone and 17β-estradiol•urea crystals have been measured at the Advanced Photon Source at Argonne National Laboratory. The experiments appeared to be unsuccessful due to an unknown instrumentation problem.

- Electron density studies at helium temperatures

We keep developing cooling techniques that will improve the stability of crystals and therefore enable us to use the benefit of very low temperatures (a vast increase in scattering power) for our electron density data sets.

- Analysis of the experimental data, comparison of the results, preparation of manuscripts

During the past year, we mainly focused our work on the treatment of already measured data sets in order to extract the most reliable and consistent information. After processing several data sets of estrogen derivatives with different biological activities, we faced an unexpected problem: the outcome partially depends on the methodology of the data treatment. Therefore, we developed a uniform approach to treat the experimental data, including the CCD data integration and the following model refinement. An optimized local atomic coordinate system has been developed before. The best way of the data treatment, the best initial approximation of a model and a uniform refinement procedure have been developed during the past year.

For example, the integration of the raw data involves integrating the intensity of the reflections as measured by a two-dimensional CCD detector. Several parameters must be defined to determine exactly how the software integrates the reflections. It was found that different detector settings, even for the same data set, require different box size parameters and profile fitting limits. The simple sum perimeter limit of 0.02 was found to be the best value for all data sets.

It was also found that the starting values for the multipole model of the electron density greatly influenced the path the refinement would take. It was determined that a specific set of starting values should be applied to each structure to ensure consistency. These optimum values were determined after preliminary refinements of several estrogen derivatives; they are shown in the **Appendices B-D**. The model parameters in the least-squares process have to be refined in small groups in order to avoid severe correlation problems associated with relatively large size of the estrogen molecules.

All this work was necessary in order to associate the differences in the electron density and electrostatic potential in estrogens with their chemical behavior, and not with differences in the data treatments. This work has been successfully completed, and now we are at the stage of comparing the final results. The re-refinements of the 3,16α,17β-estriol and estrone crystal models delayed the submission of the manuscripts prepared before. We are planning to submit them in the nearest future.

- 17β-estradiol•urea: The second measured data set appeared to be of sufficient quality. This allowed the multipole refinement to be completed as well as a full topological analysis of the electron density. The complete results are in the **Appendix B**.
- 17β-estradiol•1/2 MeOH: This system was particular challenging, because the crystal has the lowest possible symmetry, resulting in low redundancy of the data. However, the multipole refinement was successfully completed as well as a full topological analysis. The complete results are in the **Appendix C**.

- 17α-estradiol•1/2 H_2O: As it was discovered during the electron density model refinement, the hydrogen atom in the water molecule was disordered. This complicated the refinement significantly, however it was successfully completed as well as the full topological analysis. The complete results are in the **Appendix D**.
- Estrone: Based on our new developed methodology, additional work has been done in order to extract more information from the data. The experiment has been re-integrated several times in order to get the most precise structure factor list with minimum noise. Then, the model has been re-refined according to the new approach (s.a.). As a result, the two lone pairs on both oxygen atoms (Figs. 4-5, **Appendix E**) are now clearly seen. We are in a process of modifying the manuscript.
- 3,16α,17β-estriol: The data have been re-refined according to the new methodology resulting in the significant improvement of the model. The new results are reported in **Appendix F**. The manuscript has been modified.
- 17α-estradiol: The charge density study has been completed (**Appendix G**). Now we are in a process of interpreting the results.

Preliminary comparison of the results from the series of estrogen analogues showed that the core structure of the different estrogen molecules remains relatively unchanged from system to system. As the same time, the significant differences are found at the activity-sensitive molecular parts.

It was also found that each hydroxyl oxygen atom had two lone pairs in approximately sp^3 type geometry. This demonstrates that these lone pairs are surprisingly robust, and they do not significantly change in different hydrogen bonding schemes or/and when the oxygen is bound to the aromatic system. In the cases with different hydrogen bonding scheme, the electrostatic potentials around the oxygen atoms are also quite consistent.

Tasks 3-4. Extension of the above mentioned studies to the series of E_2 C-ring analogs. Electron density studies on the above mentioned estrogen analogues

We are planning to start the feasibility tests, crystallization and charge density studies of these samples shortly.

Key Research Accomplishments

- Methodology development of the X-ray CCD data treatment and model least-squares refinement:
  a) best data integration options
  b) best first approximation of the model
  c) best and uniform refinement procedure

- Charge density and electrostatic potential analysis of the 17β-estradiol•urea, 17β-estradiol•1/2 MeOH, 17α-estradiol•1/2 H_2O, estrone, 3,16α,17β-estriol, 17α-estradiol crystals

- The core estrogen structure is very consistent among different derivatives
- Parameters describing the activity-sensitive molecular parts are different
- It is possible to locate lone pair densities of oxygen's in such large systems
- The deformation electron density distributions of all hydroxyl oxygen atoms are close to sp^3 in shape, even when oxygens are bound to aromatic neighbors
- Hydroxyl oxygen lone pairs appear to be unaffected by completely different hydrogen bonding environments
- The electrostatic potentials around the oxygen atoms are consistent in the different hydrogen bonding environments

Reportable Outcomes

1. 59th Pittsburgh Diffraction Conference, Cincinnati, OH, October 25-27, 2001.

Conclusion

We have developed the methodology of the X-ray CCD data treatment and least-squares model refinement for estrogen crystals in order to extract maximum reliable and comparable information from the data. We completed charge density studies of the 17β-estradiol•urea, 17β-estradiol•1/2 MeOH, 17α-estradiol•1/2 H_2O, estrone, 3,16α,17β-estriol, 17α-estradiol crystals, performed the preliminary analysis and compared the results. We found that the deformation electron density distributions of all hydroxyl oxygen atoms are near sp^3 in shape, their lone pair densities have been reliably located. These configurations as well as the electrostatic potentials around the oxygen atoms are very consistent in the different hydrogen bonding environments. The core estrogen structure is also very consistent between the derivatives. As the same time, the significant differences are found at the activity-sensitive molecular parts.

References:

1. A.A.Pinkerton "Charge Densities from CCD Data- What Can You Believe?". 59th Pittsburgh Diffraction Conference, Cincinnati, OH, October 25-27, 2001.
2. D.A.Parrish & A.A.Pinkerton "A New Structure of 1,3,5[10]-Estratriene-3,17β-diol Solvate: Estradiol 0.66(CH_3OH) 0.33(H_2O)". Acta Cryst., 2002, submitted.

Appendix A.

A New Structure of 1,3,5[10]-Estratriene-3.17β-diol Solvate:

Estradiol 0.66(CH_3OH) 0.33(H_2O)

A New Structure of 1,3,5[10]-Estratriene-3.17β-diol Solvate: Estradiol 0.66(CH_3OH) 0.33(H_2O)

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The solvate of the steroid 17β-estradiol (E_2) with methanol (⅔) and water (⅓) is the first E_2 derivative to contain three crystallographically independent molecules in the asymmetric unit. The three steroids along with two methanol molecules and a water molecule create a three-dimensional hydrogen bonded system. Three sided columns are formed with the estradiol molecules aligning lengthwise parallel to (101) and joined by solvent molecules at both hydrophilic ends. The three estradiol molecules differ slightly in their ring bowing angles, the angle between the mean planes of the A ring and that of the BCD rings. This angle ranges from 7.1° to 12.2°.

Comment

17β-Estradiol (E_2), shown in Figure 1, is member of the estrogen family of hormones. In recent years the interest in these molecules has primarily focused on understanding their biological role in initiating breast cancer. It is well known that their ability to form hydrogen bonds in the active site of the estrogen receptor (ER) influences the biological activity. This ability to hydrogen bond has been clearly demonstrated in an array of crystal structures, especially of E_2, containing different solvent molecules or other hydrogen bond acceptors.

When comparing these structures, the flexibility of the hydrophobic region of the molecule, more specifically the B ring, becomes very apparent. Several papers have already discussed the ring bowing of this molecule[1-4]. Wiese and Brooks took it a step further in 1994, performing molecular modeling calculations on observed and novel confirmations.[5] Ivanov and coworkers performed a related study which included a larger body of compounds and more detailed analysis.[6] They conclude that there are two possible conformations very close in energy, which differ in the B-ring arrangement. Although the chance of the strained geometry binding is low, as one quarter of the binding energy (-11.9 kcal/mol) is predicted to be lost.[7] The point initially postulated by Weise and Brooks remains: the flexibility to allow bending or other conformational changes of the ligand in the receptor appear energetically achievable, and this could be an important property in determining their activity.

Molecular dynamics studies on the Ligand Binding Domain (LBD) of the ER demonstrate that the motion of LBD requires the A-ring to remain fairly steady while the CD-ring retains a higher degree of freedom.[8] The range of motion found in that study agrees very well with the reported crystal structures. It is well known that the hydrogen bonding of the ligand in the LBD causes conformational changes in the receptor. This seemingly accommodating motion of the LBD and the ligand supports the idea postulated by Weise and Brooks that the flexibility of E_2, or any other ligand which enters the LBD, could also effect the activity of the ligand. A more rigid or flexible ligand could change the natural motion of the ER complex resulting in a change in Activation Factor (AF-2) activity and therefore possibly effecting coactivator recruitment. This process is not well understood, the flexibility of the ligand is certainly only one of many physical factors associated in the activity of E_2. The structure reported here continues the trend in observing the flexibility of this molecule from a structural and hydrogen bonding view while the molecule lies in the lowest energy conformation.

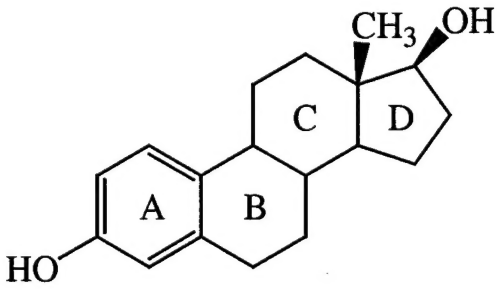

Figure 1. E_2 molecule with labeled rings.

The crystal contains three crystallographically unique E_2 molecules. The B-rings of the E_2 molecules adopt the typical conformation of a distorted 7α, 8β-half-chair and is responsible for most of the structural flexibility. Calculating the ring bowing angle as defined by Duax and Norton [9], reveals a range of 5.1° for the three molecules. Table 1 compares the ring bowing angles of the known E_2 crystal structures. The spread of over 12° with angles found distributed over the entire range indicate the shallowness of the potential associated with the bowing deformation. In a system as dynamic as the human body, the molecule would certainly have a wide range of conformations easily available.

Compound	*Mol # 1 angle*	*Mol # 2 angle*	*Mol # 3 angle*
17β-estradiol • ½ H_2O[5]	15.6	-	-
17β-estradiol • propanol[5]	12.9	-	-
17β-estradiol • urea[5]	5.6	-	-
17β-estradiol • ½ MeOH[10]	10.4	3.4	-
17β-estradiol • ⅔ MeOH • ⅓ H_2O	12.2	11.9	7.1

Table 1. Comparison of ring bowing angles in reported E_2 crystal structures (°).

The packing of this structure results in three-sided cylinders of estradiol molecules arranged parallel to (101) with the C18 methyl group pointing toward the center (Figure 2). This of course aligns the large hydrophobic regions of the molecules as well as the hydrophilic hydroxy groups. These cylinders then stack on top of each other creating three-sided columns (Figure 3) held together by hydrogen bonds involving the hydroxy groups and the three solvent molecules. A more detailed picture of the hydrogen bonding between the solvent and E_2 molecules can be seen in Figure 4 and from Table 2. There is also an inter-columnar hydrogen bond which occurs between the water molecule and a 3-hydroxy group. This, along with the inter-columnar hydrogen bonded solvent, creates a hydrophilic layer which is approximately 30° from perpendicular to the columns (Figure 5). Structurally, all bond lengths and angles are in expected ranges.

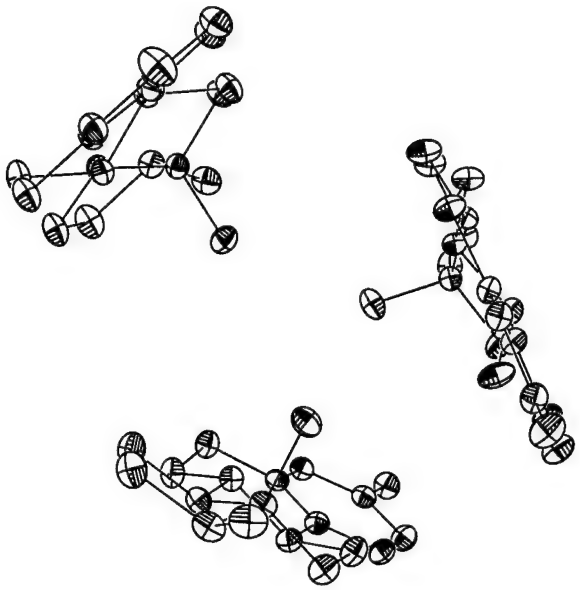

Figure 2. Molecular arrangement of E_2 looking down the three sided column.

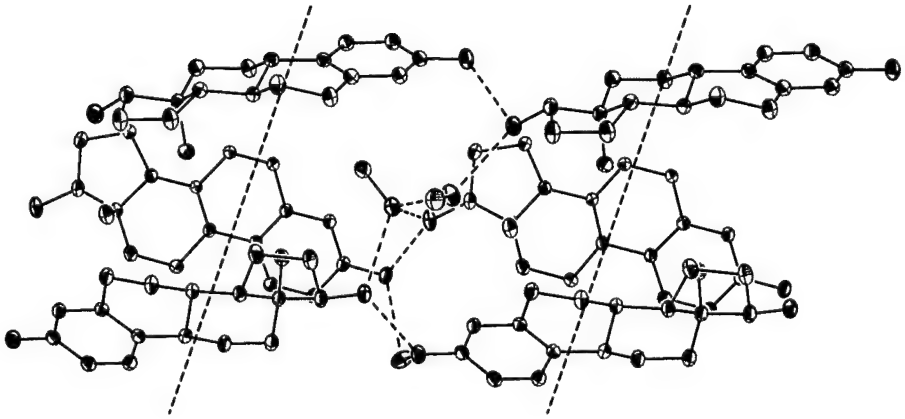

Figure 3. Packing of E_2 groups with hydrogen bonded solvent molecules viewed perpendicular to the columns. Dotted lines indicate the region detailed in Figure 4, oxygen atoms are in red.

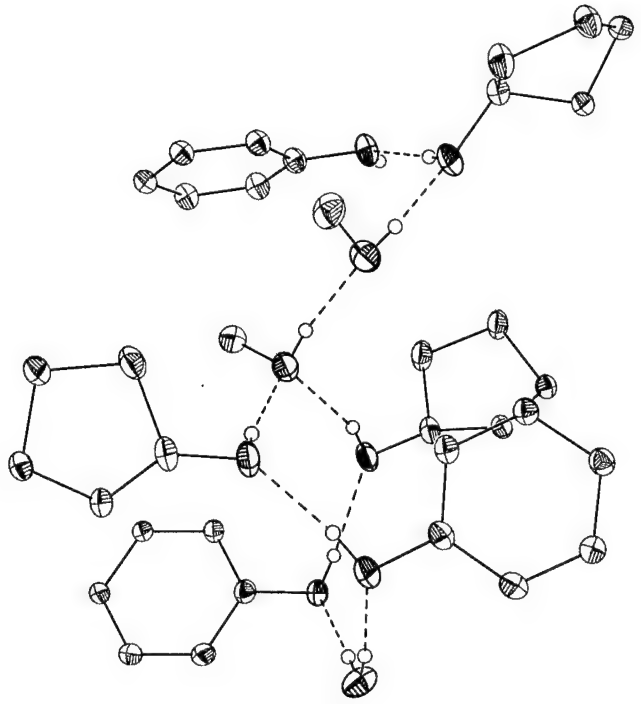

Figure 4. Hydrogen bonded region of the column, including solvent molecules and only the A or D rings of E_2. Oxygen atoms are in red, hydrogen atoms in green.

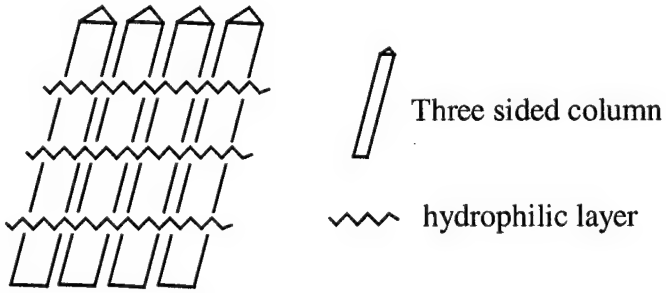

Figure 5. Schematic of packed columns and the relation to the hydrophilic layer containing the hydroxy groups and the solvent molecules.

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O1A—H1OA···O2A^{i}	0.74(3)	1.89(3)	2.6226(17)	171(3)
O1B—H1OB···O2B^{i}	0.85(3)	1.83(3)	2.6654(18)	171(3)
O1C—H1OC···O3	0.76(3)	1.82(3)	2.5767(18)	170(3)
O2A—H2OA···O4B	0.76(3)	1.97(3)	2.7017(18)	162(2)
O2B—H2OB···O4B^{ii}	0.73(2)	2.06(2)	2.7823(19)	168(2)
O2C—H2OC···O1C^{iii}	0.73(2)	1.99(3)	2.7169(17)	175(3)
O3—H3OA···O1A^{iv}	0.72(4)	2.02(4)	2.7430(20)	178(4)
O3—H3OB···O1B^{v}	0.76(3)	2.04(3)	2.7926(19)	173(3)
O4A—H4OA···O2C	0.83(3)	1.85(3)	2.6809(18)	174(3)
O4B—H4OB···O4A^{vi}	0.78(2)	1.88(2)	2.6462(17)	166(2)

Symmetry codes: (i) 1 + x, y, 1 + z; (ii) –3 - x, ½ + y, -2 - z; (iii) x - 1, y, z - 1; (iv) -x, ½ + y, -z; (v) 1 + x, y, z; (vi) x - 1, y, z

Table 2. Hydrogen bonding geometry (Å, °).

Experimental

Crystals were grown by slow evaporation from a methanol solution open to the air. It is presumed that the methanol was either wet prior to use in this experiment or absorbed atmospheric moisture. Crystals were grown over the course of 3 days, and harvested when reaching the appropriate size.

Preliminary examination and data collection were performed at 298(2) K on a Siemens SMART Platform diffractometer equipped with a 2K CCD detector located 6.12cm from the crystal. 0.3° Omega scans were carried out at three different phi settings and a detector position of -25° in 2θ, corresponding to a nominal sphere of data, with the frame time set at 30 seconds. The unit cell was initially refined with the SMART Software Package.[11] The final unit cell was obtained from the refinement of 7309 reflections after integration (SAINT 6).[12] The intensity data were corrected for decay and absorption (SADABS).[13] The structure was solved by direct methods and refined using the SHELXTL program package.[14] All non-hydrogen atoms were refined with anisotropic displacement parameters by full matrix least-squares on F^2. All hydrogen atoms on the solvent molecules and the hydroxy groups of the E_2 molecules were located in the difference map. The other hydrogen atoms were included with idealized geometries. All hydrogen atoms were refined with isotropic displacement parameters.

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Appendix B.

17β-estradiol•urea

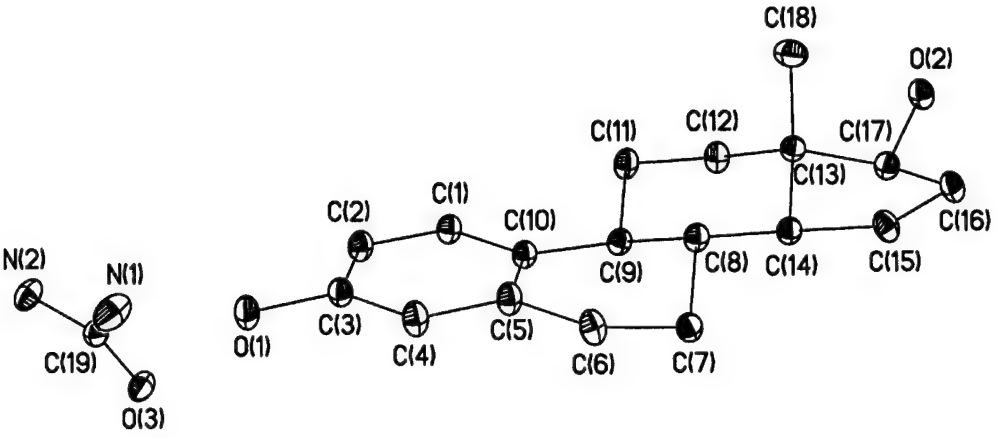

Figure 1. Thermal ellipsoid plot of 17β-estradiol•urea where ellipsoids represent 50% probability electron density of the atom. Hydrogen atoms are omitted for clarity.

Run	2θ	ω	ϕ	Scan Width (°)	# of Frames	Frame Times (sec)
1	-10	0	45	-0.30	606	60
2	-10	0	135	-0.30	606	60
3	-10	0	225	-0.30	606	60
4	-10	0	315	-0.30	606	60
5	-10	0	45	-0.30	50	60
6	-50	-40	0	-0.30	606	180
7	-50	-40	90	-0.30	606	180
8	-50	-40	180	-0.30	606	180
9	-50	-40	270	-0.30	606	180
10	-50	-40	0	-0.30	50	180
11	-85	-75	22	-0.30	606	180
12	-85	-75	112	-0.30	606	180
13	-85	-75	202	-0.30	606	180
14	-85	-75	292	-0.30	606	180
15	-85	-75	22	-0.30	50	180

Table 1. Data collection parameters for 17β-estradiol•urea.

Crystal Data			
Chemical Formula	$C_{19}H_{28}N_2O_3$		
Temperature	100.0(1) K		
Crystal Dimensions	0.35 x 0.37 x 0.40 mm		
Space Group	$P2_12_12_1$		
A	7.9022(9) Å		
B	9.2228(10) Å		
C	24.5890(28) Å		
Volume	1792.06(56) $Å^3$		
Z (Crystallographic)	4		
Integration Parameters			
	Box Size (°)	Profile Fitting (I/σ)	Simple Sum Perimeter Limit
Low Angle	1.5 x 1.5 x 1.0	30 10	0.02
Medium Angle	1.2 x 1.2 x 0.8	30 10	0.02
High Angle	1.0 x 1.0 x 0.6	20 10	0.02
Reflection Statistics (from SORTAV)			
Total Reflections	110999		
Rejected Outliers	779		
Unique Reflections	13187		
Average Redundancy	8.4		
Resolution	1.180 $Å^{-1}$		
Completeness	98.6 %		
R_1	3.52 %		
R_2	3.98 %		
R_w	12.84 %		
Z (Refinement)	1.999		

Table 2. Selected crystal, integration, and reflection data for 17β-estradiol•urea.

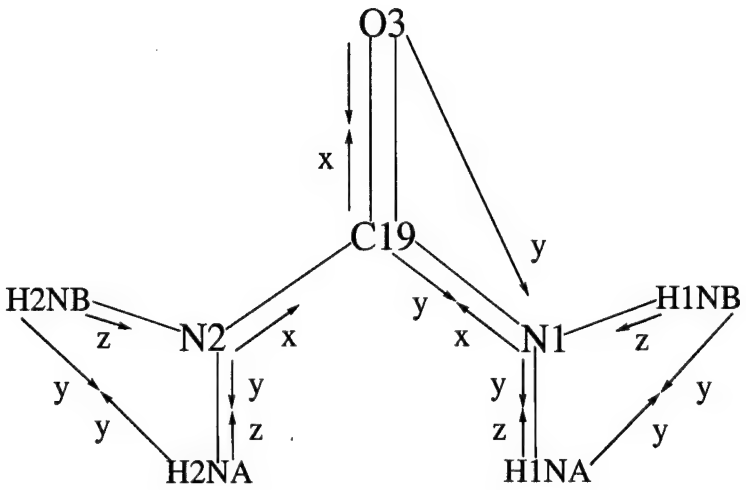

Figure 2. Coordinate system for the urea molecule.

	n	m	$\langle n \rangle$	R_1	R_2	R_w	Z	V
Q < -4	0	0	0.0	0.0000	0.0000	0.0000	0.000	0.000
-4 < Q < -3	0	0	0.0	0.0000	0.0000	0.0000	0.000	0.000
-3 < Q < -2	0	0	0.0	0.0000	0.0000	0.0000	0.000	0.000
-2 < Q < -1	16	4	4.0	0.5725	0.6015	0.6289	0.924	0.623
-1 < Q < 0	477	118	4.0	1.0875	1.1169	1.0735	1.563	3.758
0 < Q < 1	5750	1091	5.3	0.9343	0.8988	0.8687	1.928	1.597
1 < Q < 2	9331	1649	5.7	0.5575	0.6002	0.5627	1.972	0.654
2 < Q < 3	7669	1278	6.0	0.3519	0.4088	0.3630	2.085	0.391
3 < Q < 4	5953	928	6.4	0.2593	0.3163	0.2643	2.148	0.282
4 < Q < 6	10295	1418	7.3	0.1823	0.2246	0.1892	2.234	0.197
6 < Q < 8	10833	1229	8.8	0.1302	0.1642	0.1397	2.143	0.143
8 < Q < 10	8050	873	9.2	0.1012	0.1272	0.1088	1.990	0.111
10 < Q < 20	22630	2179	10.4	0.0604	0.0737	0.0725	1.867	0.069
20 < Q < 30	13284	1022	13.0	0.0358	0.0498	0.0412	1.337	0.039
30 < Q < 50	15702	984	16.0	0.0236	0.0339	0.0267	1.037	0.027
50 < Q < 100	629	34	18.5	0.0153	0.0216	0.0165	0.975	0.017
100 < Q	0	0	0.0	0.0000	0.0000	0.0000	0.000	0.000

Table 3. Intensity-Significance Intervals where n is the number of reflections, m is the number of unique reflections, $\langle n \rangle$ is the average measurement multiplicity, and Q=I/Max ($\sigma_{int}/\sigma_{ext}$) respectively for 17$\beta$-estradiol•urea.

	n	m	$\langle n \rangle$	R_1	R_2	R_w	Z	V
D > 1.150	16117	750	21.5	0.0265	0.0399	0.1067	2.013	0.029
1.150 > D > 0.913	9979	699	14.3	0.0259	0.0300	0.1044	1.958	0.031
0.913 > D > 0.798	5817	694	8.4	0.0347	0.0332	0.1071	2.010	0.040
0.798 > D > 0.725	6582	677	9.7	0.0399	0.0382	0.1048	2.012	0.045
0.725 > D > 0.673	8411	672	12.5	0.0482	0.0468	0.1053	2.012	0.055
0.673 > D > 0.633	8720	683	12.8	0.0633	0.0612	0.1137	1.962	0.071
0.633 > D > 0.601	7909	653	12.1	0.0681	0.0590	0.1197	2.020	0.077
0.601 > D > 0.575	7635	663	11.5	0.0872	0.0793	0.1287	2.037	0.097
0.575 > D > 0.553	6763	677	10.0	0.1040	0.0949	0.1445	2.002	0.117
0.553 > D > 0.534	3653	650	5.6	0.1328	0.1375	0.1650	2.042	0.143
0.534 > D > 0.517	3549	642	5.5	0.1489	0.1390	0.1797	2.031	0.167
0.517 > D > 0.502	3458	641	5.4	0.1718	0.1567	0.2036	2.100	0.190
0.502 > D > 0.489	3268	623	5.2	0.2044	0.1875	0.2255	2.066	0.220
0.489 > D > 0.477	3261	650	5.0	0.2160	0.1968	0.2254	2.078	0.232
0.477 > D > 0.466	3002	607	4.9	0.1970	0.1732	0.2134	2.035	0.215
0.466 > D > 0.456	3000	628	4.8	0.2063	0.1610	0.2306	1.955	0.231
0.456 > D > 0.447	2929	614	4.8	0.2780	0.2531	0.2829	1.951	0.307
0.447 > D > 0.439	2646	590	4.5	0.3363	0.3255	0.3274	2.009	0.378
0.439 > D > 0.431	2466	599	4.1	0.3174	0.3091	0.3151	1.957	0.357
0.431 > D > 0.424	1454	395	3.7	0.3788	0.3783	0.3699	2.020	0.435

Table 4. Equal-Volume Resolution Shells where n is the number of reflections, m is the number of unique reflections, $\langle n \rangle$ is the average measurement multiplicity, and D=sinθ/λ (Å^{-1}) respectively for 17β-estradiol•urea.

	Monopole	sp^2		sp^3
		20	33+	32-
O1	-0.50			
O2	-0.49			
C1	-0.30	-0.22	0.34	
C2	-0.38	-0.19	0.37	
C3	0.27	-0.21	0.38	
C4	-0.33	-0.17	0.36	
C5	-0.18	-0.22	0.33	
C6	-0.26			0.31
C7	-0.31			0.34
C8	-0.21			0.39
C9	-0.17			0.31
C10	-0.25	-0.18	0.37	
C11	-0.31			0.35
C12	-0.28			0.31
C13	-0.16			0.38
C14	-0.20			0.38
C15	-0.26			0.33
C16	-0.35			0.42
C17	0.20			0.38
C18	-0.32			0.27

	Monopole
H1O	0.40
H2O	0.38
H1	0.23
H2	0.22
H4	0.26
H6x	0.20
H7x	0.17
H8	0.20
H9	0.16
H11x	0.17
H12x	0.16
H14	0.19
H15x	0.16
H16x	0.18
H17	0.13
H18x	0.18

Atoms	Kappa	κ	κ'
O1, O2	1	0.97	1.16
C3	2	1.01	0.92
C17	3	1.02	0.95
C1, C2, C4	4	0.97	0.92
C5, C10	5	0.98	0.87
C6, C7, C8, C9, C11, C12, C13, C14, C15, C16, C17, C18	6	0.98	0.95
all C-H hydrogen atoms	7	1.20	1.29
H1O, H2O	8	1.20	1.29
C19	9	0.97	1.00
O3	10	0.98	1.00
N1, N2	11	0.98	1.00
all N-H hydrogen atoms	12	1.02	1.29

Table 5. Starting values entered into the model for the multipole refinement for 17β-estradiol•urea. Units for multipole populations are e^-.

Atom	X	Y	Z
O1	-0.42058(4)	-0.59511(3)	-0.23303(1)
O2	-0.84199(4)	-0.41994(3)	0.18983(1)
C1	-0.04796(5)	-0.97596(4)	-0.22247(1)
C2	-0.37746(5)	-0.60179(4)	-0.13757(1)
C3	-0.48608(5)	-0.58215(4)	-0.18160(1)
C4	-0.65568(5)	-0.55015(4)	-0.17217(1)
C5	-0.71969(5)	-0.54141(4)	-0.11928(1)
C6	-0.90360(5)	-0.50057(6)	-0.11255(2)
C7	-0.97324(5)	-0.53270(5)	-0.05588(1)
C8	-0.84925(5)	-0.48092(4)	-0.01225(1)
C9	-0.68421(5)	-0.57011(4)	-0.01689(1)
C10	-0.61320(5)	-0.56620(3)	-0.07447(1)
C11	-0.55545(5)	-0.52954(4)	0.02735(1)
C12	-0.63109(5)	-0.53975(4)	0.08481(1)
C13	-0.79262(5)	-0.44893(3)	0.08951(1)
C14	-0.91843(5)	-0.49685(4)	0.04520(1)
C15	-1.08387(5)	-0.41986(5)	0.06157(2)
C16	-1.07772(5)	-0.41828(5)	0.12477(2)
C17	-0.90256(5)	-0.48028(4)	0.13965(1)
C18	-0.75013(6)	-0.28663(4)	0.08704(2)
O3	-0.04796(4)	-0.97596(3)	-0.22247(1)
N1	-0.09659(6)	-0.74930(4)	-0.25468(2)
N2	0.16786(5)	-0.85170(4)	-0.26106(2)
C19	0.00538(5)	-0.86273(4)	-0.24498(1)

Atom	X	Y	Z
H1O	-0.5100(10)	-0.5903(7)	-0.2600(3)
H2O	-0.7423(10)	-0.4751(7)	0.2000(3)
H1	-0.3549(9)	-0.6105(6)	-0.0517(2)
H2	-0.2452(9)	-0.6251(7)	-0.1443(3)
H4	-0.7400(8)	-0.5358(6)	-0.2063(2)
H6A	-0.9774(9)	-0.5601(7)	-0.1426(3)
H6B	-0.9100(9)	-0.3835(7)	-0.1182(3)
H7A	-0.9929(9)	-0.6490(6)	-0.0510(2)
H7B	-1.0948(9)	-0.4788(6)	-0.0504(2)
H8	-0.8208(8)	-0.3662(7)	-0.0205(2)
H9	-0.7189(8)	-0.6835(6)	-0.0087(2)
H11A	-0.4469(9)	-0.6024(7)	0.0259(2)
H11B	-0.5063(8)	-0.4209(6)	0.0200(2)
H12A	-0.6637(9)	-0.6524(6)	0.0932(2)
H12B	-0.5379(8)	-0.5075(6)	0.1152(2)
H14	-0.9378(9)	-0.6138(6)	0.0513(2)
H15A	-1.1956(9)	-0.4791(7)	0.0481(3)
H15B	-1.0837(9)	-0.3087(6)	0.0465(2)
H16A	-1.1756(9)	-0.4867(7)	0.1426(3)
H16B	-1.0881(9)	-0.3060(7)	0.1382(2)
H17	-0.9091(7)	-0.5985(6)	0.1453(2)
H18A	-0.6610(9)	-0.2590(7)	0.1175(3)
H18B	-0.8580(9)	-0.2196(7)	0.0920(3)
H18C	-0.6952(9)	-0.2570(6)	0.0493(2)
H1NA	-0.0501(9)	-0.6536(8)	-0.2679(3)
H1NB	-0.2166(11)	-0.7532(7)	-0.2406(3)
H2NA	0.2092(9)	-0.7646(7)	-0.2821(3)
H2NB	0.2465(9)	-0.9373(7)	-0.2569(2)

Table 6. Fractional atomic coordinates for 17β-estradiol•urea.

Atom	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.01219(10)	0.02443(12)	0.01244(9)	0.00174(11)	0.00131(8)	-0.00125(8)
O2	0.01461(11)	0.02036(11)	0.01108(9)	0.00249(10)	-0.00183(8)	-0.00162(8)
C1	0.00957(12)	0.01862(13)	0.01219(12)	0.00164(11)	-0.00066(10)	0.00125(10)
C2	0.00983(13)	0.02011(14)	0.01349(12)	0.00185(12)	0.00006(10)	0.00039(10)
C3	0.01021(13)	0.01712(13)	0.01145(11)	0.00099(12)	0.00042(10)	-0.00055(9)
C4	0.01090(13)	0.02641(16)	0.01081(12)	0.00325(13)	-0.00012(10)	-0.00051(10)
C5	0.00961(13)	0.02420(15)	0.01106(12)	0.00309(12)	-0.00084(10)	-0.00021(10)
C6	0.01117(14)	0.04863(26)	0.01159(13)	0.00858(18)	-0.00129(11)	0.00116(14)
C7	0.00921(13)	0.02872(17)	0.01277(12)	0.00087(14)	-0.00135(10)	-0.00267(11)
C8	0.00961(12)	0.01643(12)	0.01109(11)	0.00090(11)	-0.00096(10)	0.00023(9)
C9	0.00978(12)	0.01527(12)	0.01158(11)	0.00015(11)	-0.00077(9)	0.00087(9)
C10	0.00897(12)	0.01541(12)	0.01155(11)	0.00117(11)	-0.00080(9)	0.00038(9)
C11	0.00970(13)	0.02408(16)	0.01227(12)	0.00005(13)	-0.00152(10)	0.00010(11)
C12	0.01189(13)	0.02230(15)	0.01171(12)	0.00316(13)	-0.00168(10)	0.00088(10)
C13	0.01115(13)	0.01363(12)	0.01124(11)	-0.00017(11)	-0.00106(10)	-0.00017(9)
C14	0.01021(13)	0.01698(13)	0.01142(11)	-0.00030(11)	-0.00072(10)	-0.00060(9)
C15	0.01228(15)	0.03705(21)	0.01294(13)	0.00648(16)	-0.00145(11)	-0.00237(13)
C16	0.01284(15)	0.03791(21)	0.01290(13)	0.00506(16)	-0.00006(12)	-0.00300(13)
C17	0.01249(14)	0.01785(13)	0.01145(11)	0.00011(13)	-0.00036(10)	-0.00014(10)
C18	0.02583(21)	0.01531(13)	0.01719(15)	-0.00386(14)	-0.00059(14)	-0.00085(11)
O3	0.01596(12)	0.01799(11)	0.02292(12)	-0.00185(11)	0.00584(10)	0.00228(9)
N1	0.01700(17)	0.01705(14)	0.04896(23)	0.00427(14)	0.00785(17)	0.00300(14)
N2	0.01356(14)	0.01725(13)	0.02797(15)	0.00033(12)	0.00619(12)	0.00426(11)
C19	0.01344(15)	0.01475(12)	0.01804(13)	-0.00048(12)	0.00345(12)	-0.00102(10)

Table 7. Anisotropic thermal parameters of non-H atoms for 17β-estradiol•urea.

Atom	U_{iso}
H1O	0.0232(16)
H2O	0.0252(17)
H1	0.0499(16)
H2	0.0456(16)
H4	0.0406(15)
H6A	0.0711(19)
H6B	0.0651(18)
H7A	0.0524(16)
H7B	0.0506(15)
H8	0.0465(15)
H9	0.0482(16)
H11A	0.0613(17)
H11B	0.0479(14)
H12A	0.0544(16)
H12B	0.0524(15)

Atom	U_{iso}
H14	0.0401(14)
H15A	0.0637(18)
H15B	0.0531(16)
H16A	0.0675(19)
H16B	0.0570(17)
H17	0.0501(14)
H18A	0.0631(18)
H18B	0.0629(17)
H18C	0.0596(17)
H1NA	0.0471(18)
H1NB	0.0509(19)
H2NA	0.0437(17)
H2NB	0.0448(17)

Table 8. Isotropic thermal parameters of H atoms for 17β-estradiol•urea.

Atoms	Bond Length (Å)
O1 – C3	1.3716(4)
O2 – C17	1.4357(4)
C1 – C2	1.3923(5)
C1 – C10	1.4013(5)
C2 – C3	1.3934(5)
C3 – C4	1.3918(5)
C4 – C5	1.3977(5)
C5 – C6	1.5104(6)
C5 – C10	1.4051(5)
C6 – C7	1.5272(5)
C7 – C8	1.5294(5)
C8 – C9	1.5461(5)
C8 – C14	1.5219(5)

Atoms	Bond Length (Å)
C9 – C10	1.5235(5)
C9 – C11	1.5357(5)
C11 – C12	1.5368(5)
C12 – C13	1.5312(5)
C13 – C14	1.5398(5)
C13 – C17	1.5357(5)
C13 – C18	1.5352(5)
C14 – C15	1.5412(6)
C15 – C16	1.5550(5)
C16 – C17	1.5417(6)
O3 – C19	1.2547(5)
N1 – C19	1.3419(6)
N2 – C19	1.3474(5)

Table 9. Bond distances of non-H atoms of 17β-estradiol•urea.

Atoms	Bond Angle (°)
C3 – O1 – H1O	110.6(5)
C17 – O2 – H2O	106.7(5)
C2 – C1 – C10	122.3(1)
C2 – C1 – H1	117.6(4)
C10 – C1 – H1	120.1(4)
C1 – C2 – C3	119.3(1)
C1 – C2 – H2	120.5(4)
C3 – C2 – H2	120.2(4)
O1 – C3 – C2	118.2(1)
O1 – C3 – C4	122.4(1)
C2 – C3 – C4	119.4(1)
C3 – C4 – C5	121.0(1)
C3 – C4 – H4	119.4(4)
C5 – C4 – H4	119.5(4)
C4 – C5 – C6	117.7(1)
C4 – C5 – C10	120.2(1)
C6 – C5 – C10	122.1(1)
C5 – C6 - C7	113.5(1)
C5 – C6 – H6A	108.3(4)
C5 – C6 – H6B	106.1(4)
C7 – C6 – H6A	109.2(4)
C7 – C6 – H6B	106.9(4)
H6A – C6 – H6B	112.8(6)
C6 – C7 – C8	110.4(1)
C6 – C7 – H7A	110.0(4)
C6 – C7 – H7B	110.0(3)
C8 – C7 – H7A	108.8(4)
C8 – C7 – H7B	109.6(4)
H7A – C7 – H7B	108.0(5)
C7 – C8 – C9	108.8(1)
C7 – C8 – C14	113.0(1)
C9 – C8 – C14	108.7(1)
C7 – C8 – H8	107.6(4)
C9 – C8 – H8	109.0(4)

Atoms	Bond Angle (°)
C14 – C8 – H8	109.7(3)
C8 – C9 – C10	111.5(1)
C8 – C9 – C11	112.2(1)
C10 – C9 – C11	114.1(1)
C8 – C9 – H9	106.4(4)
C10 – C9 – H9	106.6(4)
C11 – C9 – H9	105.4(4)
C1 – C10 – C5	117.6(1)
C1 – C10 – C9	121.5(1)
C5 – C10 – C9	120.8(1)
C9 – C11 – C12	112.2(1)
C9 – C11 – H11A	110.4(4)
C9 – C11 – H11B	110.0(3)
C12 – C11 – H11A	107.3(4)
C12 – C11 – H11B	110.4(3)
H11A – C11 – H11B	106.3(5)
C11 – C12 – C13	111.1(1)
C11 – C12 – H12A	109.0(4)
C11 – C12 – H12B	110.5(4)
C13 – C12 – H12A	108.0(4)
C13 – C12 – H12B	111.2(4)
H12A – C12 – H12B	106.8(5)
C12 – C13 – C14	109.1(1)
C12 – C13 – C17	115.4(1)
C12 – C13 – C18	110.4(1)
C14 – C13 – C17	98.6(1)
C14 – C13 – C18	113.1(1)
C17 – C13 – C18	109.8(1)
C8 – C14 – C13	113.4(1)
C8 – C14 – C15	120.2(1)
C13 – C14 – C15	103.3(1)
C8 – C14 – H14	105.8(3)
C13 – C14 – H14	105.9(4)
C15 – C14 – H14	107.3(4)

Atoms	Bond Angle (°)
C14 – C15 – C16	103.8(1)
C14 – C15 – H15A	112.1(4)
C14 – C15 – H15B	110.1(4)
C16 – C15 – H15A	109.5(4)
C16 – C15 – H15B	109.3(4)
H15A – C15 – H15B	111.7(6)
C15 – C16 – C17	105.2(1)
C15 – C16 – H16A	111.9(4)
C15 – C16 – H16B	108.1(4)
C17 – C16 – H16A	109.1(4)
C17 – C16 – H16B	110.4(4)
H16A – C16 – H16B	112.0(6)
O2 – C17 – C13	115.4(1)
O2 – C17 – C16	111.1(1)
C13 – C17 – C16	104.3(1)
O2 – C17 – H17	106.9(3)
C13 – C17 – H17	108.3(3)
C16 – C17 – H17	110.8(4)
C13 – C18 – H18A	110.6(4)
C13 – C18 – H18B	112.8(4)
C13 – C18 – H18C	112.1(4)
H18A – C18 – H18B	108.2(6)
H18A – C18 – H18C	106.6(6)
H18B – C18 – H18C	106.2(6)
O3 – C19 – N1	121.7(1)
O3 – C19 – N2	120.8(1)
N1 – C19 – N2	121.4(1)
C19 – N1 – H1NA	118.4(5)
C19 – N1 – H1NB	118.9(5)
H1NA – N1 – H1NB	121.2(6)
C19 – N2 – H2NA	121.4(5)
C19 – N2 – H2NB	119.8(5)
H2NA – N2 – H2NB	118.4(6)

Table 10. Bond angles of 17β-estradiol•urea.

Atom	Monopole Population ($P_{0,0}$)
O1	6.534(9)
O2	6.527(9)
C1	4.233(16)
C2	4.227(16)
C3	3.852(14)
C4	4.267(15)
C5	4.110(15)
C6	4.265(16)
C7	4.279(16)
C8	4.121(14)
C9	4.131(15)
C10	4.106(15)
C11	4.277(15)
C12	4.273(15)
C13	4.158(16)
C14	4.111(14)
C15	4.294(15)
C16	4.273(16)
C17	3.832(13)
C18	4.402(17)
O3	6.234(9)
N1	5.282(12)
N2	5.286(11)
C19	4.030(14)

Atom	Monopole Population ($P_{0,0}$)
H1O	0.599(9)
H2O	0.609(9)
H1	0.794(10)
H2	0.752(9)
H4	0.751(9)
H6A	0.853(7)
H6B	0.853(7)
H7A	0.854(7)
H7B	0.854(7)
H8	0.820(9)
H9	0.820(9)
H11A	0.853(7)
H11B	0.853(7)
H12A	0.859(7)
H12B	0.859(7)
H14	0.824(8)
H15A	0.851(7)
H15B	0.851(7)
H16A	0.854(7)
H16B	0.854(7)
H17	0.880(9)
H18A	0.878(6)
H18B	0.878(6)
H18C	0.878(6)
H1NA	0.795(10)
H1NB	0.791(11)
H2NA	0.793(10)
H2NB	0.792(10)

Table 11. Monopole populations (e^-) of 17β-estradiol•urea.

Multipoles	O1	O2	O3	N1	N2
$P_{1,+1}$	-0.017(8)	-0.069(7)	-0.095(6)	0.037(10)	0.0
$P_{1,-1}$	0.0	-0.029(7)	-0.021(6)	0.0	-0.011(10)
$P_{1,0}$	0.0	0.023(7)	-0.016(5)	0.051(8)	-0.040(7)
$P_{2,0}$	0.089(8)	0.078(8)	-0.089(7)	-0.048(9)	-0.032(8)
$P_{2,+1}$	-0.013(8)	0.026(8)	0.0	-0.051(10)	0.018(9)
$P_{2,-1}$	-0.023(9)	0.035(7)	0.043(7)	0.0	0.0
$P_{2,+2}$	-0.036(8)	-0.047(8)	-0.073(7)	0.045(10)	0.0
$P_{2,-2}$	0.0	0.015(8)	-0.018(8)	0.0	0.0
$P_{3,0}$	0.0	0.056(14)	0.031(11)	0.049(13)	-0.043(12)
$P_{3,+1}$	-0.037(10)	0.0	0.017(10)	0.061(12)	-0.060(12)
$P_{3,-1}$	-0.051(10)	-0.052(10)	-0.041(10)	0.0	0.0
$P_{3,+2}$	0.027(14)	-0.011(10)	0.0	-0.084(15)	0.0
$P_{3,-2}$	0.031(14)	0.0	0.0	-0.024(13)	0.024(12)
$P_{3,+3}$	0.101(10)	0.069(12)	0.0	0.155(11)	0.167(10)
$P_{3,-3}$	-0.059(11)	-0.028(10)	0.018(10)	0.0	0.0
$P_{4,0}$	0.041(13)	-0.031(14)			
$P_{4,+1}$	-0.036(13)	0.022(13)			
$P_{4,-1}$	0.0	0.016(13)			
$P_{4,+2}$	-0.025(13)	0.038(12)			
$P_{4,-2}$	0.0	-0.017(12)			
$P_{4,+3}$	0.029(14)	-0.025(13)			
$P_{4,-3}$	0.0	0.0			
$P_{4,+4}$	0.020(12)	0.020(12)			
$P_{4,-4}$	-0.020(12)	-0.042(13)			

Table 12. Multipole populations (e^-) of Oxygen and Nitrogen atoms of 17β-estradiol•urea.

Multipoles	C1	C2	C3	C4	C5	C6	C7	C8	C9
$P_{1,+1}$	0.069(15)	0.073(14)	0.037(16)	0.0	0.052(16)	-0.074(13)	-0.057(13)	0.013(12)	0.035(12)
$P_{1,-1}$	0.0	-0.038(15)	0.067(14)	0.046(16)	0.052(16)	0.0	0.0	0.0	0.0
$P_{1,0}$	0.0	0.019(13)	0.0	-0.041(13)	-0.058(14)	-0.092(13)	-0.047(12)	0.013(12)	0.069(13)
$P_{2,0}$	-0.228(11)	-0.189(11)	-0.191(11)	-0.192(11)	-0.231(12)	-0.042(15)	-0.012(12)	0.0	0.056(13)
$P_{2,+1}$	0.0	0.0	0.0	0.023(13)	-0.038(14)	-0.037(12)	-0.019(11)	0.0	0.023(12)
$P_{2,-1}$	0.048(13)	0.021(13)	0.036(12)	0.0	0.0	0.059(12)	0.0	0.0	0.0
$P_{2,+2}$	0.057(14)	0.0	0.054(14)	0.062(14)	0.047(15)	0.105(12)	0.071(11)	0.023(11)	0.023(12)
$P_{2,-2}$	0.0	0.067(14)	-0.059(14)	-0.056(14)	0.023(15)	0.022(13)	0.0	-0.015(12)	0.0
$P_{3,0}$	-0.034(16)	-0.022(16)	0.0	0.0	-0.029(18)	-0.064(17)	0.034(17)	0.050(18)	0.048(17)
$P_{3,+1}$	-0.042(15)	0.0	0.0	0.0	0.043(17)	0.022(18)	-0.166(15)	0.0	0.046(17)
$P_{3,-1}$	0.021(15)	0.0	0.022(15)	0.0	0.023(17)	0.0	0.015(14)	0.0	0.177(15)
$P_{3,+2}$	-0.024(20)	0.018(20)	0.0	0.0	0.056(23)	0.035(16)	0.0	0.0	-0.116(16)
$P_{3,-2}$	-0.025(20)	0.034(17)	-0.074(22)	0.036(19)	0.0	0.310(15)	0.254(15)	0.388(15)	0.320(15)
$P_{3,+3}$	0.365(15)	0.328(15)	0.351(15)	0.342(15)	0.313(15)	-0.208(15)	-0.189(16)	0.027(15)	0.120(15)
$P_{3,-3}$	-0.036(19)	0.0	0.075(22)	0.050(19)	0.0	-0.029(17)	0.0	-0.031(17)	0.0

Multipoles	C10	C11	C12	C13	C14	C15	C16	C17	C18	C19
$P_{1,+1}$	0.068(18)	-0.079(13)	-0.017(12)	0.0	-0.045(14)	-0.052(14)	-0.051(14)	-0.019(11)	0.066(11)	0.145(14)
$P_{1,-1}$	-0.028(15)	-0.050(11)	-0.034(13)	0.059(13)	0.035(12)	0.077(12)	-0.023(13)	0.042(12)	0.024(12)	-0.023(16)
$P_{1,0}$	-0.026(13)	0.011(11)	0.0	-0.030(12)	-0.084(13)	-0.079(12)	-0.096(12)	-0.071(12)	0.0	-0.059(13)
$P_{2,0}$	-0.230(11)	0.0	0.0	-0.020(12)	-0.014(12)	-0.038(13)	-0.092(11)	0.0	-0.052(12)	-0.377(12)
$P_{2,+1}$	-0.020(15)	-0.053(12)	0.038(11)	-0.026(12)	0.035(12)	0.033(11)	0.0	0.069(11)	0.043(12)	0.0
$P_{2,-1}$	0.021(13)	0.019(11)	0.033(13)	0.0	0.0	0.023(12)	0.020(13)	0.0	0.0	-0.022(13)
$P_{2,+2}$	0.060(15)	0.063(11)	0.039(12)	0.0	0.034(11)	0.083(12)	0.068(12)	0.020(11)	0.022(10)	0.166(15)
$P_{2,-2}$	-0.036(15)	-0.032(11)	0.052(12)	0.0	-0.043(13)	-0.020(12)	-0.016(11)	0.0	-0.011(11)	0.0
$P_{3,0}$	0.060(16)	0.026(15)	0.018(14)	0.0	-0.023(17)	0.054(19)	-0.045(16)	-0.041(15)	-0.023(15)	0.0
$P_{3,+1}$	-0.031(17)	-0.111(16)	-0.105(14)	0.0	-0.049(16)	0.0	0.0	-0.110(14)	0.0	-0.082(16)
$P_{3,-1}$	0.036(15)	-0.027(14)	-0.037(17)	0.0	0.061(16)	0.055(16)	0.064(17)	0.028(16)	0.0	-0.074(18)
$P_{3,+2}$	-0.023(20)	-0.058(16)	0.040(16)	0.066(17)	0.026(16)	0.0	-0.029(18)	0.073(15)	0.023(18)	-0.020(19)
$P_{3,-2}$	-0.082(24)	0.351(16)	0.375(15)	0.472(15)	0.334(14)	0.330(15)	0.337(15)	0.329(14)	0.265(14)	0.025(19)
$P_{3,+3}$	0.358(16)	-0.173(14)	-0.100(16)	0.035(17)	-0.105(17)	-0.170(16)	-0.130(16)	-0.022(16)	0.049(13)	0.500(18)
$P_{3,-3}$	0.038(24)	0.0	0.0	-0.025(18)	-0.056(16)	0.0	0.017(16)	-0.042(15)	-0.050(13)	0.0

Table 13. Multipole populations (e^-) of Carbon atoms of 17β-estradiol•urea.

Atoms	$P_{1,0}$	$P_{2,0}$
H1O	0.130(11)	0.023(14)
H2O	0.121(11)	0.026(14)
H1	0.152(13)	0.0
H2	0.117(13)	0.026(15)
H4	0.172(12)	0.0
H6A	0.131(9)	0.052(10)
H6B	0.131(9)	0.052(10)
H7A	0.117(9)	0.036(10)
H7B	0.117(9)	0.036(10)
H8	0.148(11)	0.113(15)
H9	0.106(12)	0.023(15)
H11A	0.122(8)	0.040(11)
H11B	0.122(8)	0.040(11)
H12A	0.138(8)	0.0
H12B	0.138(8)	0.0
H14	0.076(11)	0.047(13)
H15A	0.105(8)	0.035(11)
H15B	0.105(8)	0.035(11)
H16A	0.131(8)	0.044(11)
H16B	0.131(8)	0.044(11)
H17	0.183(11)	0.076(15)
H18A	0.126(6)	-0.032(9)
H18B	0.126(6)	-0.032(9)
H18C	0.126(6)	-0.032(9)
H1NA	0.152(14)	0.077(17)
H1NB	0.164(15)	0.025(18)
H2NA	0.162(13)	0.0
H2NB	0.189(13)	0.097(19)

Table 14. Multipole populations (e^-) of Hydrogen atoms of 17β-estradiol•urea.

Bond	$\rho(r_c)$	$\nabla^2\rho(r_c)$	R_{ij}	d_1	d_2	λ_1	λ_2	λ_3	ε
O1 – C3	2.087	-18.278	1.3735	0.8406	0.5328	-16.40	-15.05	13.17	0.09
O1 – H1O	2.283	-34.847	0.9701	0.7549	0.2152	-37.51	-37.10	39.76	0.01
O2 – C17	1.739	-7.066	1.4361	0.8207	0.6155	-12.61	-11.76	17.30	0.07
O2 – H2O	2.221	-30.002	0.9702	0.7490	0.2212	-35.29	-35.22	40.50	0.00
C1 – C2	2.188	-21.224	1.3923	0.7537	0.6387	-16.15	-13.34	8.26	0.21
C1 – C10	2.184	-20.509	1.4015	0.6771	0.7244	-16.21	-13.19	8.89	0.23
C1 – H1	1.945	-17.399	1.0805	0.6484	0.4321	-17.84	-16.23	16.67	0.10
C2 – C3	2.201	-20.558	1.3942	0.6970	0.6972	-16.73	-13.50	9.67	0.24
C2 – H2	1.947	-17.412	1.0801	0.6725	0.4076	-18.63	-16.82	18.03	0.11
C3 – C4	2.238	-21.298	1.3919	0.6954	0.6965	-17.37	-13.58	9.66	0.28
C4 – C5	2.144	-19.321	1.3977	0.7275	0.6702	-15.37	-12.94	8.99	0.19
C4 – H4	1.890	-17.235	1.0801	0.6420	0.4381	-17.00	-15.60	15.37	0.09
C5 – C6	1.753	-12.498	1.5104	0.7542	0.7562	-11.87	-10.85	10.22	0.09
C5 – C10	2.073	-17.563	1.4056	0.7242	0.6815	-15.00	-11.83	9.27	0.27
C6 – C7	1.671	-10.333	1.5286	0.7841	0.7445	-10.68	-10.23	10.57	0.04
C6 – H6A	1.831	-12.619	1.0908	0.6435	0.4473	-16.09	-13.33	16.81	0.11
C6 – H6B	1.831	-12.619	1.0908	0.6435	0.4473	-16.09	-13.33	16.81	0.11
C7 – C8	1.655	-9.901	1.5299	0.7729	0.7570	-10.35	-10.04	10.48	0.03
C7 – H7A	1.899	-15.061	1.0906	0.6524	0.4382	-16.77	-15.49	17.19	0.08
C7 – H7B	1.857	-14.569	1.0914	0.6503	0.4411	-16.31	-15.35	17.09	0.06
C8 – C9	1.642	-10.327	1.5466	0.7799	0.7667	-10.36	-10.25	10.28	0.01
C8 – C14	1.653	-10.798	1.5222	0.7755	0.7467	-10.81	-10.02	10.03	0.08
C8 – H8	1.937	-19.600	1.1001	0.6447	0.4554	-17.43	-16.44	14.27	0.06
C9 – C10	1.667	-10.503	1.5240	0.7527	0.7714	-10.93	-9.81	10.24	0.11
C9 – C11	1.701	-11.816	1.5360	0.7469	0.7891	-11.33	-10.80	10.31	0.05
C9 – H9	1.900	-15.526	1.1001	0.6725	0.4276	-17.18	-15.99	17.64	0.07

Table 15. Topological properties of bond critical points in 17β-estradiol•urea.

Bond	$\rho(r_c)$	$\nabla^2\rho(r_c)$	R_{ij}	d_1	d_2	λ_1	λ_2	λ_3	ε
C11 – C12	1.625	-10.611	1.5370	0.7554	0.7816	-10.64	-10.04	10.06	0.06
C11 – H11A	1.881	-15.797	1.0915	0.6470	0.4445	-16.59	-15.64	16.44	0.06
C11 – H11B	1.965	-16.576	1.0900	0.6560	0.4340	-17.75	-16.24	17.42	0.09
C12 – C13	1.752	-12.334	1.5312	0.7736	0.7576	-11.75	-10.99	10.41	0.07
C12 – H12A	1.857	-14.791	1.0903	0.6392	0.4511	-15.65	-15.34	16.19	0.02
C12 – H12B	1.906	-15.838	1.0900	0.6430	0.4471	-16.66	-15.56	16.38	0.07
C13 – C14	1.678	-10.846	1.5405	0.7759	0.7647	-10.60	-10.46	10.21	0.01
C13 – C17	1.663	-10.699	1.5358	0.7920	0.7438	-11.24	-10.15	10.69	0.11
C13 – C18	1.643	-10.505	1.5353	0.7848	0.7505	-10.43	-10.33	10.26	0.01
C14 – C15	1.576	-8.910	1.5423	0.7492	0.7931	-10.33	-8.94	10.37	0.16
C14 – H14	1.833	-13.737	1.1001	0.6774	0.4227	-16.23	-15.71	18.21	0.03
C15 – C16	1.629	-10.671	1.5555	0.7848	0.7707	-10.72	-10.25	10.30	0.05
C15 – H15A	1.927	-14.910	1.0912	0.6642	0.4270	-17.76	-15.56	18.41	0.14
C15 – H15B	1.680	-10.886	1.0926	0.6398	0.4528	-14.44	-12.82	16.37	0.13
C16 – C17	1.636	-9.386	1.5418	0.7812	0.7606	-10.89	-9.84	11.34	0.11
C16 – H16A	1.917	-15.675	1.0909	0.6486	0.4422	-17.37	-15.14	16.84	0.15
C16 – H16B	1.774	-13.036	1.0948	0.6419	0.4529	-15.39	-14.15	16.50	0.09
C17 – H17	2.064	-20.314	1.1003	0.6508	0.4495	-19.34	-18.25	17.28	0.06
C18 – H18A	1.862	-12.496	1.0608	0.6180	0.4428	-15.33	-14.17	17.01	0.08
C18 – H18B	1.922	-13.177	1.0602	0.6249	0.4353	-16.19	-14.80	17.81	0.09
C18 – H18C	1.878	-13.292	1.0602	0.6181	0.4421	-15.73	-14.50	16.94	0.08
O3 – C19	2.767	-31.828	1.2548	0.8156	0.4392	-24.24	-23.53	15.94	0.03
N1 – C19	2.261	-24.734	1.3424	0.8749	0.4675	-17.80	-16.90	9.97	0.05
N2 – C19	2.266	-24.089	1.3476	0.8745	0.4731	-18.03	-15.38	9.32	0.17
N1 – H1NA	2.407	-28.058	1.0101	0.7172	0.2929	-31.73	-30.39	34.06	0.04
N1 – H1NB	2.370	-23.814	1.0100	0.7135	0.2965	-30.34	-28.21	34.74	0.08
N2 – H2NA	2.333	-21.488	1.0100	0.7113	0.2987	-29.51	-27.12	35.14	0.09
N2 – H2NB	2.494	-31.772	1.0100	0.7153	0.2947	-33.39	-31.38	33.00	0.06

Table 16. Topological properties of bond critical points in 17β-estradiol•urea continued.

Bond	$\rho(r_c)$	$\nabla^2\rho(r_c)$	R_{ij}	d_1	d_2	λ_1	λ_2	λ_3	ε
O2—**H2O··O3**	0.230	4.624	1.6951	0.5589	1.1362	-1.47	-1.42	7.52	0.04
O1—**H1O··O2**	0.208	4.795	1.7027	0.5510	1.1516	-1.27	-1.18	7.24	0.08
N1—**H1NA··O3**	0.210	2.909	1.8274	0.6530	1.1744	-1.34	-1.31	5.57	0.02
N1—**H1NB··O1**	0.085	1.751	2.2050	0.8369	1.3681	-0.42	-0.34	2.51	0.24
N2—**H2NB··O1**	0.129	1.702	2.0179	0.7221	1.2957	-0.79	-0.73	3.23	0.08
N2—**H2NA··O2**	0.064	2.101	2.1200	0.7459	1.3740	-0.31	-0.24	2.66	0.29

Table 17. Topological properties of bond critical points in the hydrogen bonds of 17β-estradiol•urea.

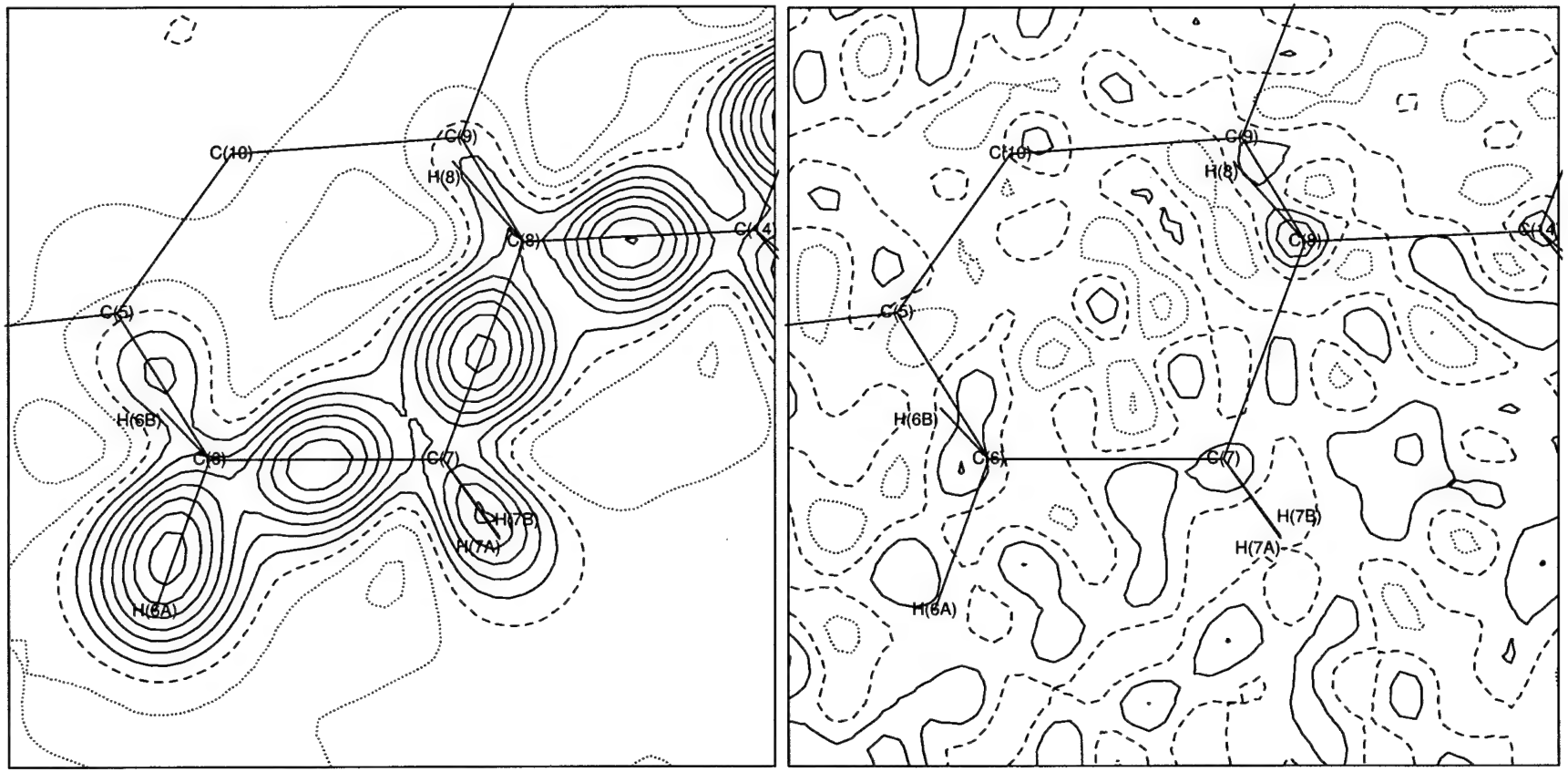

Figure 3. Dynamic model map and residual map in the C6 – C7 – C8 plane of 17β-estradiol•urea. Contour intervals are 0.05 eÅ^{-3} with solid lines positive, dashed lines zero, and dotted lines negative.

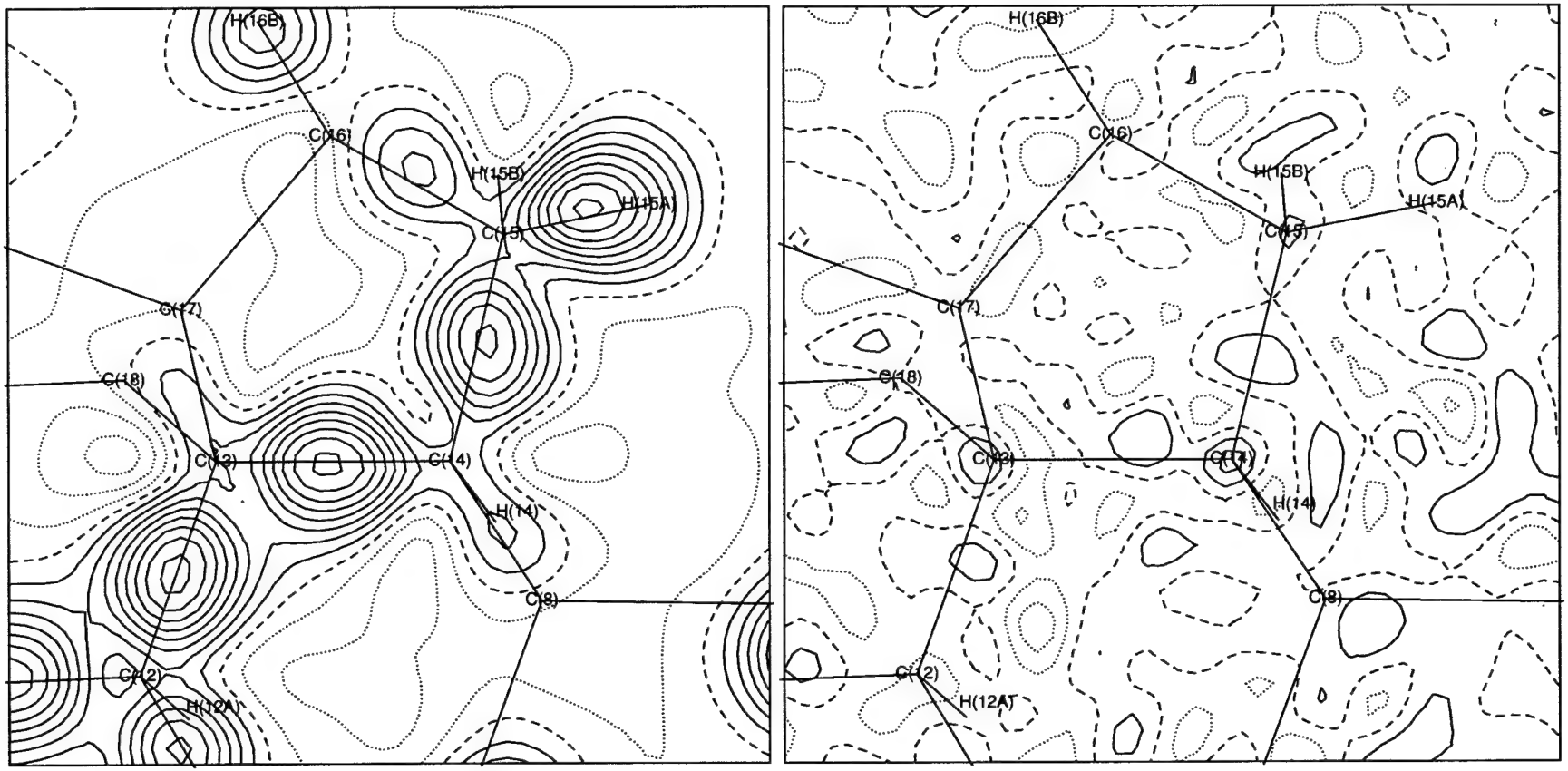

Figure 4. Dynamic model map and residual map in the C13 – C14 – C15 plane of 17β-estradiol•urea. Contour intervals are 0.05 e$\AA^{-3}$ with solid lines positive, dashed lines zero, and dotted lines negative.

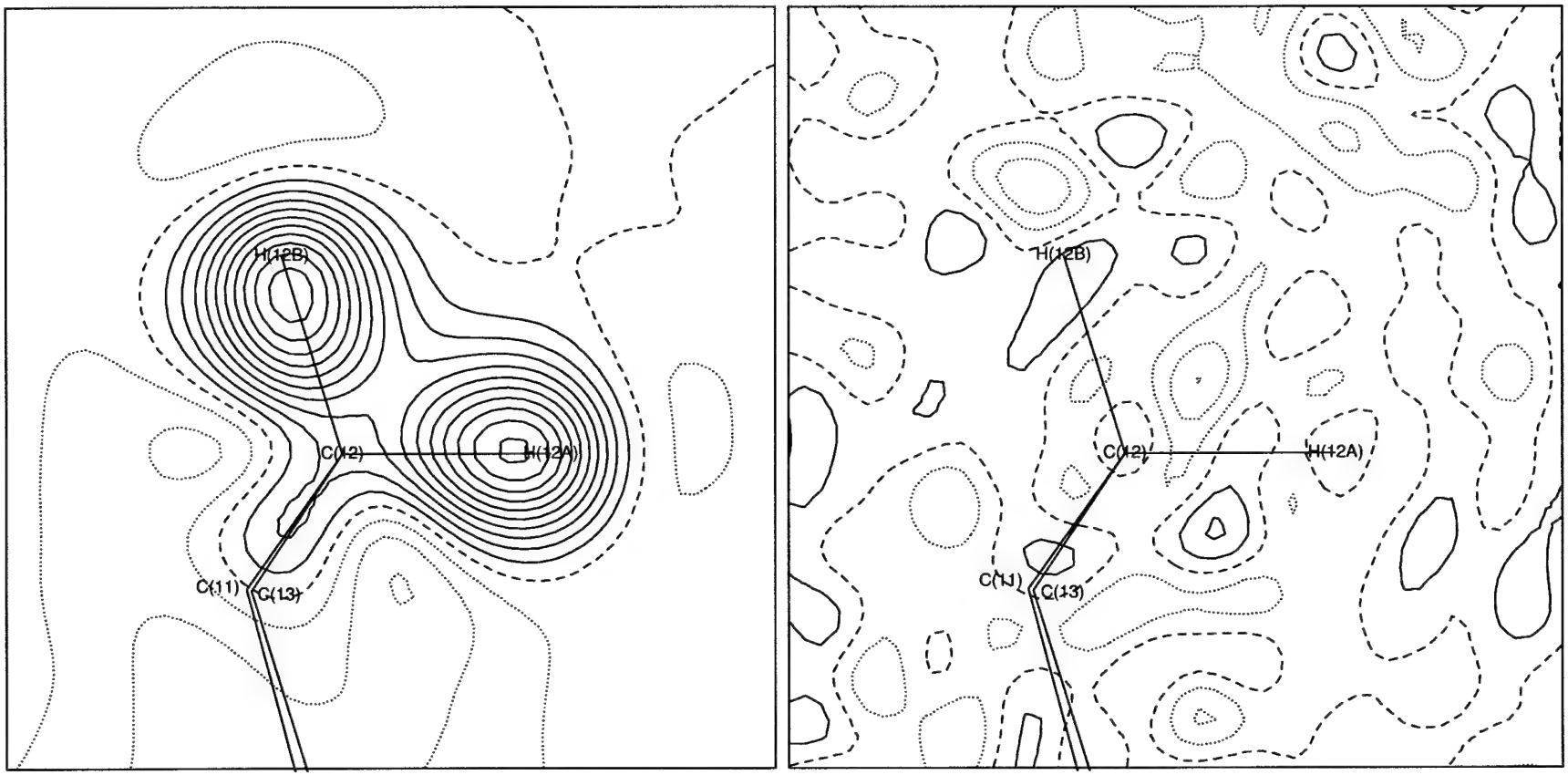

Figure 5. Dynamic model map and residual map in the C12 – H12A – H12B plane of 17β-estradiol•urea. Contour intervals are 0.05 eÅ^{-3} with solid lines positive, dashed lines zero, and dotted lines negative.

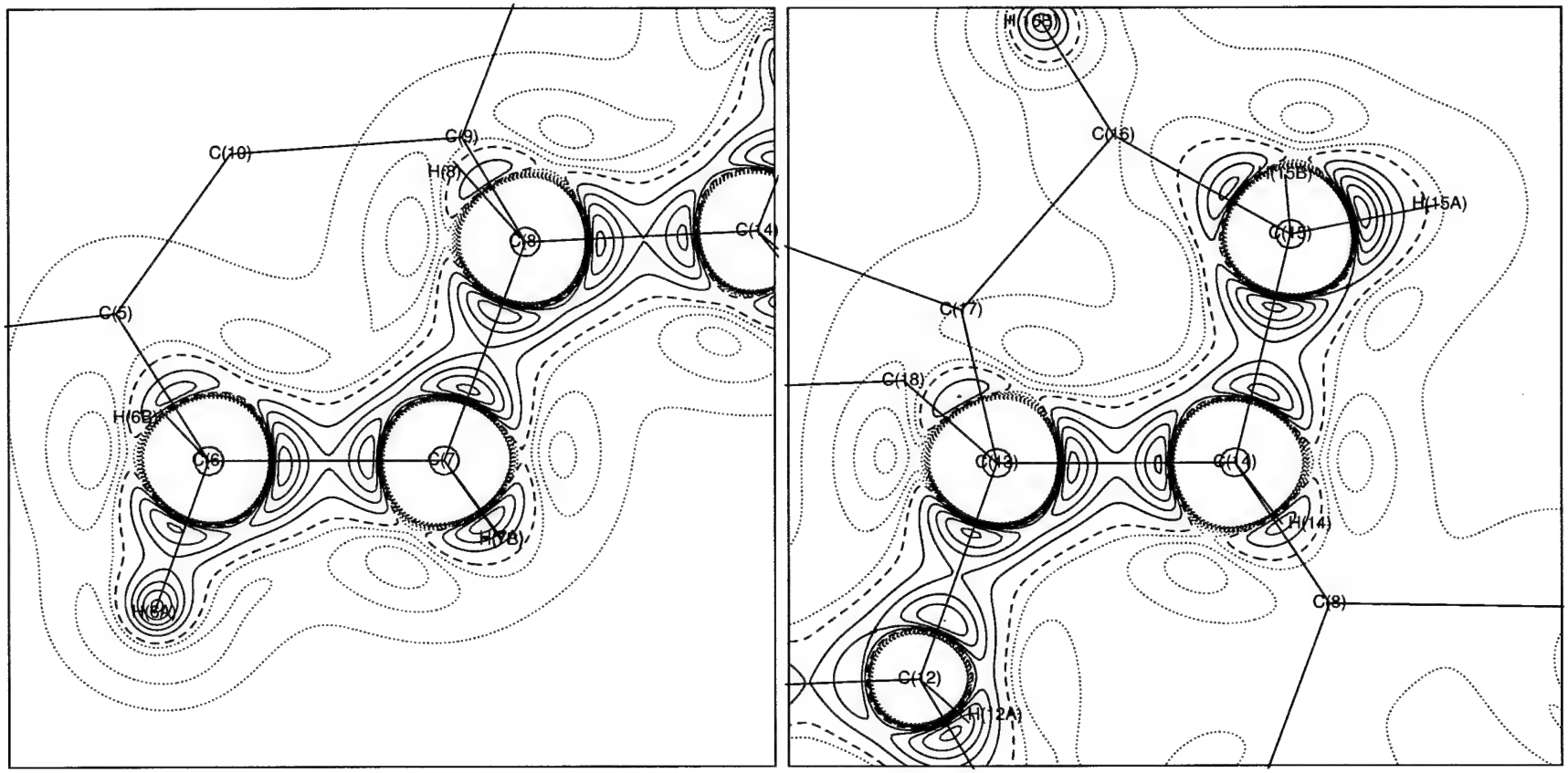

Figure 6. The Laplacian of the total electron density of atoms at rest in the C6 – C7 – C8 and C13 – C14 – C15 planes of 17β-estradiol•urea. Contour intervals are 5 eÅ^{-5} starting at 5 eÅ^{-5} (solid blue lines), -2 eÅ^{-5} starting at -2 eÅ^{-5} (dotted red lines), and the dashed line equals 0 eÅ^{-5}.

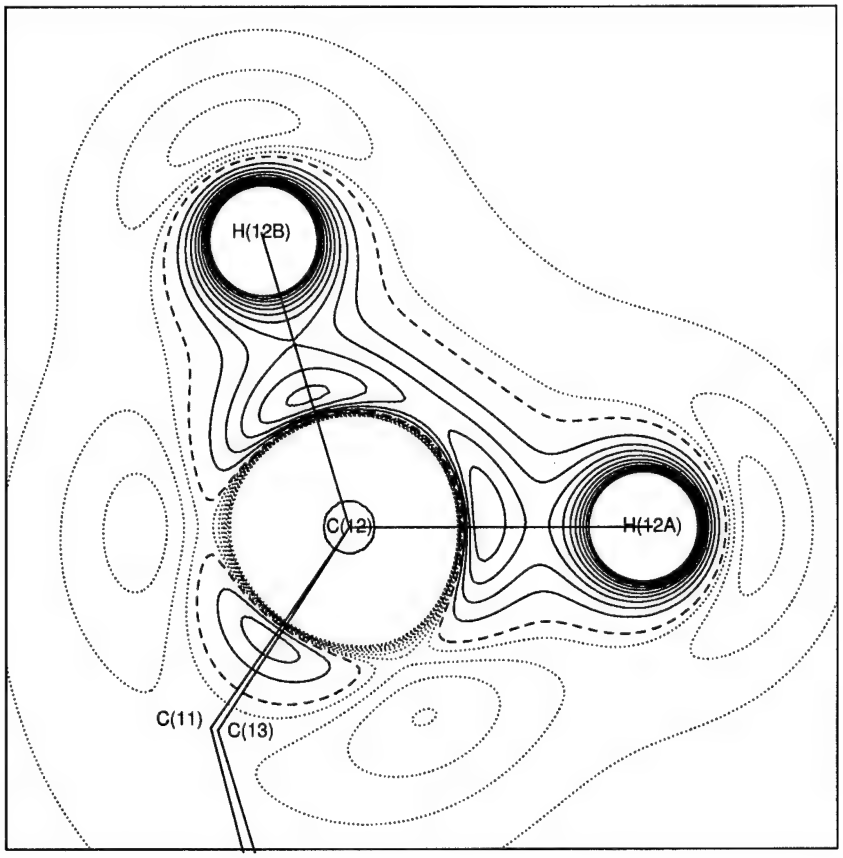

Figure 7. The Laplacian of the total electron density of atoms at rest in the H12A – C12 – H12B plane of 17β-estradiol•urea. Contour intervals are 5 eÅ^{-5} starting at 5 eÅ^{-5} (solid blue lines), -2 eÅ^{-5} starting at -2 eÅ^{-5} (dotted red lines), and the dashed line plots 0 eÅ^{-5}.

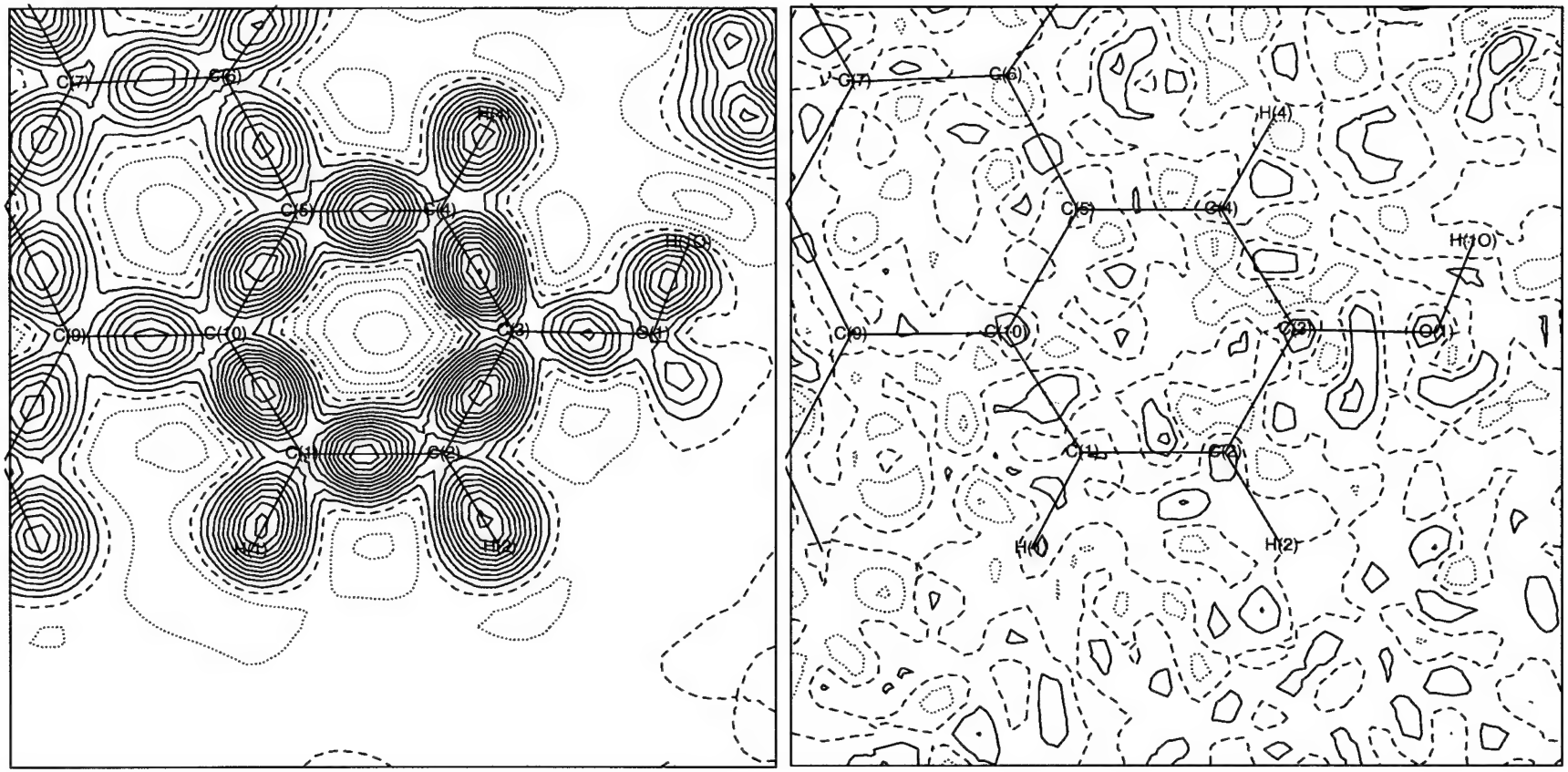

Figure 8. Dynamic model map and residual map in the plane of the aromatic ring of 17β-estradiol•urea. Contour intervals are 0.05 eÅ^{-3} with solid lines positive, dashed lines zero, and dotted lines negative.

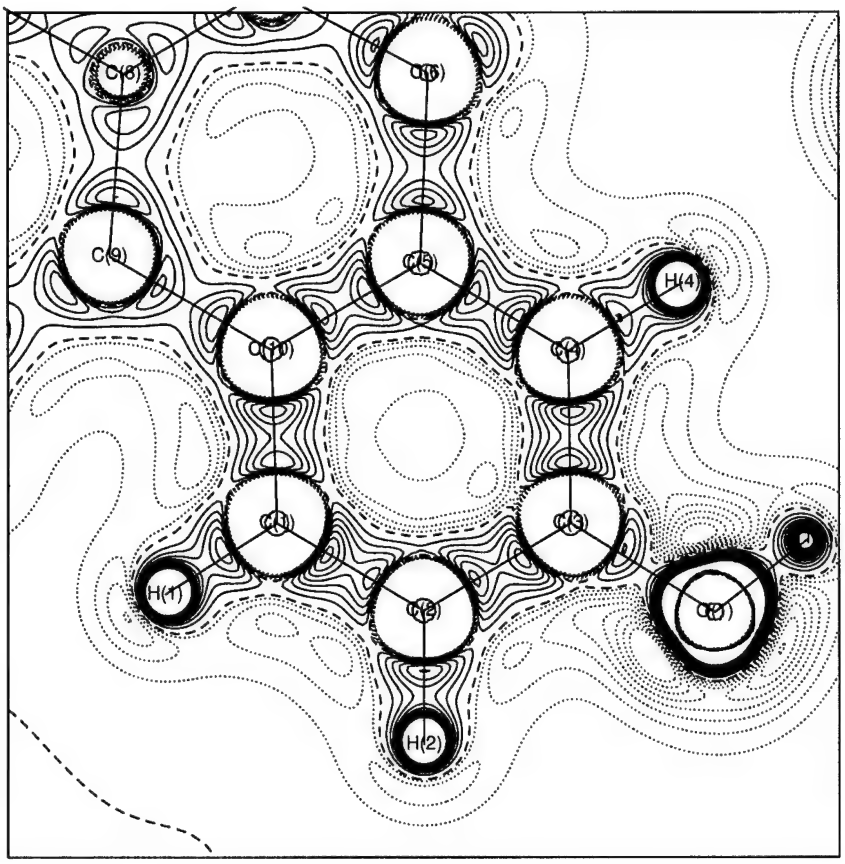

Figure 9. The Laplacian of the total electron density of atoms at rest in the plane of the aromatic ring of 17β-estradiol•urea. Contour intervals are 5 eÅ^{-5} starting at 5 eÅ^{-5} (solid blue lines), -2 eÅ^{-5} starting at -2 eÅ^{-5} (dotted red lines), and the dashed line plots 0 eÅ^{-5}.

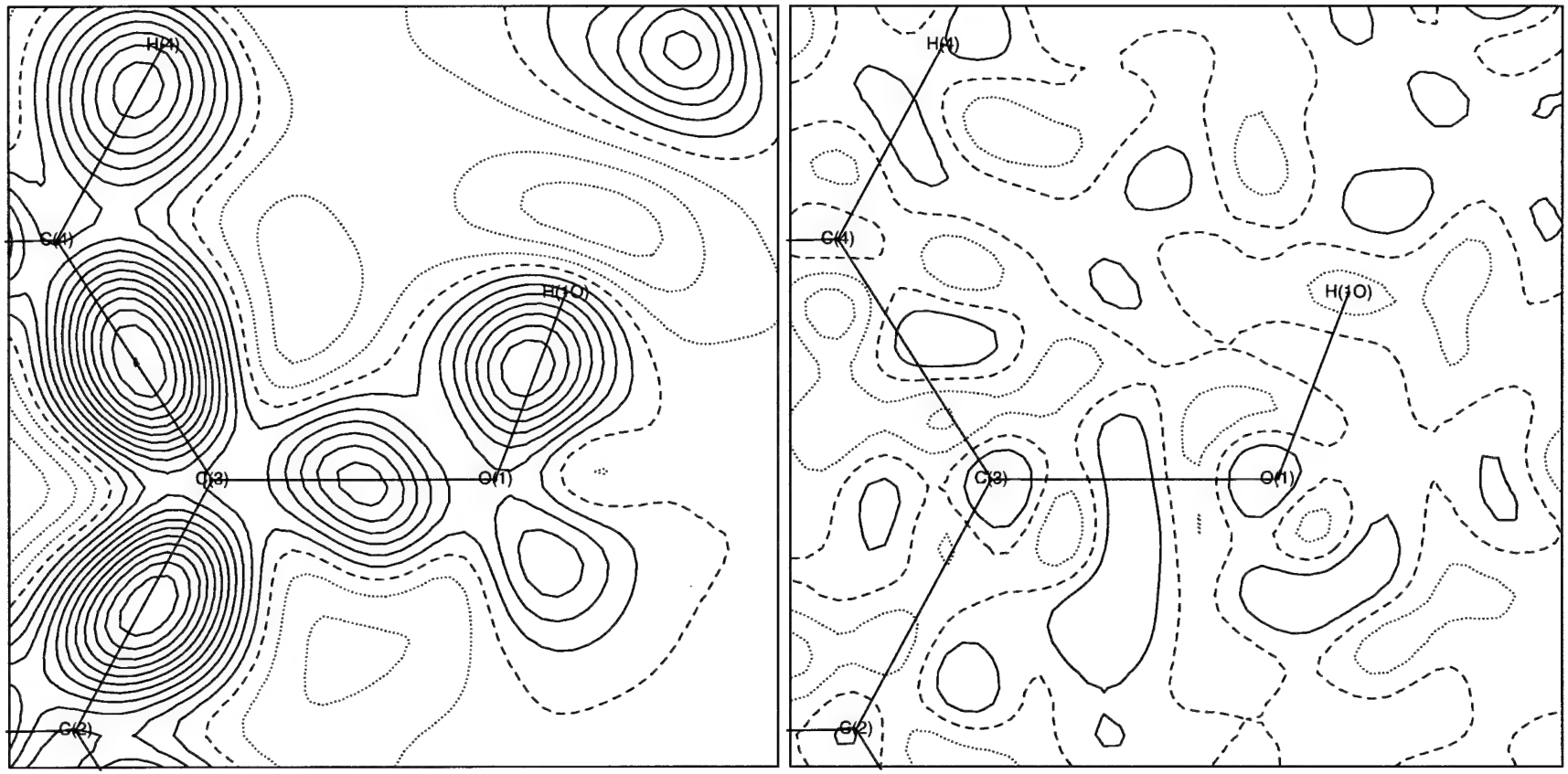

Figure 10. Dynamic model map and residual map in the C3 – O1 – H1O plane of 17β-estradiol•urea. Contour intervals are 0.05 eÅ^{-3} with solid lines positive, dashed lines zero, and dotted lines negative.

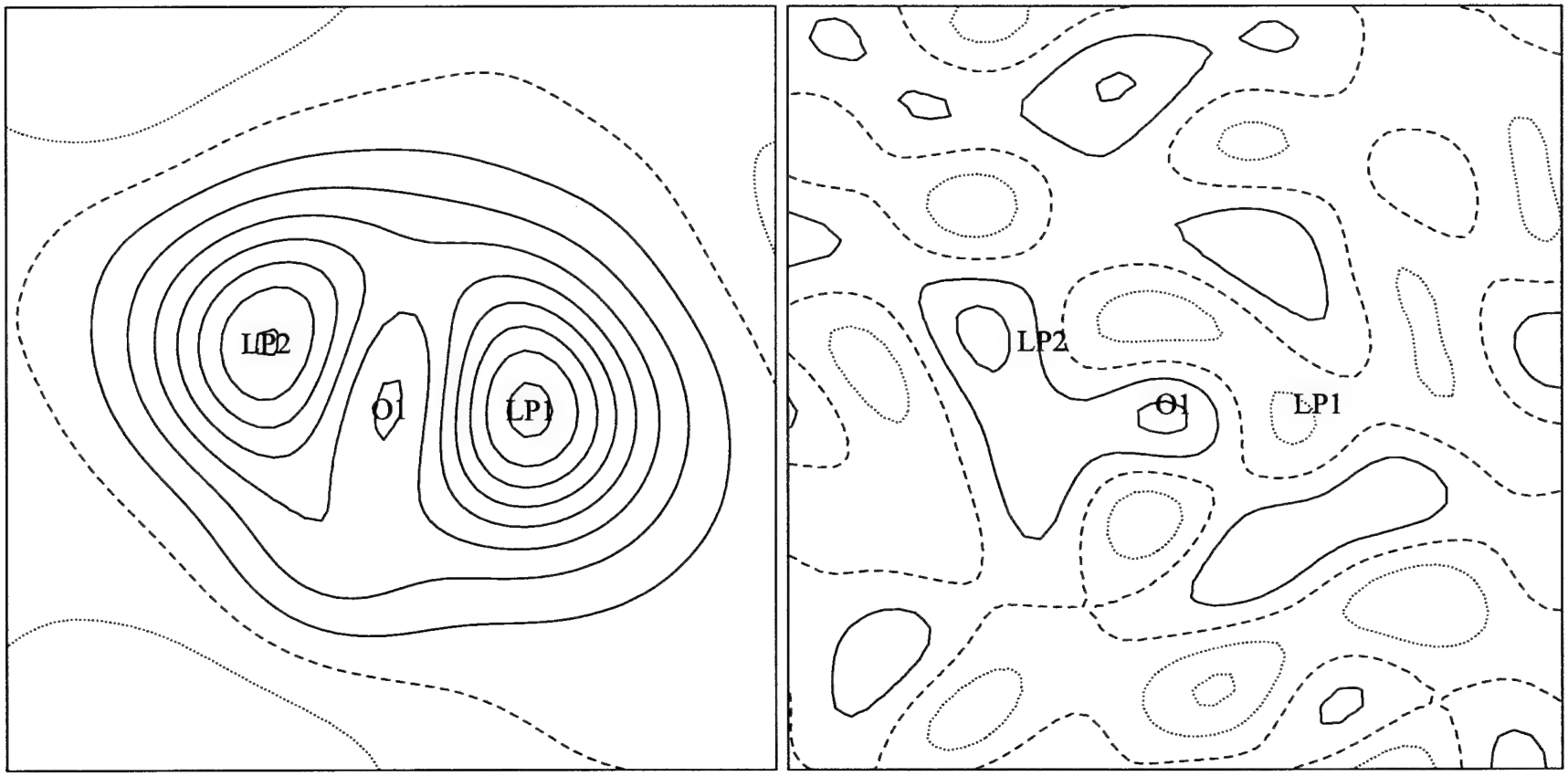

Figure 11. Dynamic model map and residual map in the plane of the lone pairs of O1 of 17β-estradiol•urea. Contour intervals are 0.05 eÅ^{-3} with solid lines positive, dashed lines zero, and dotted lines negative.

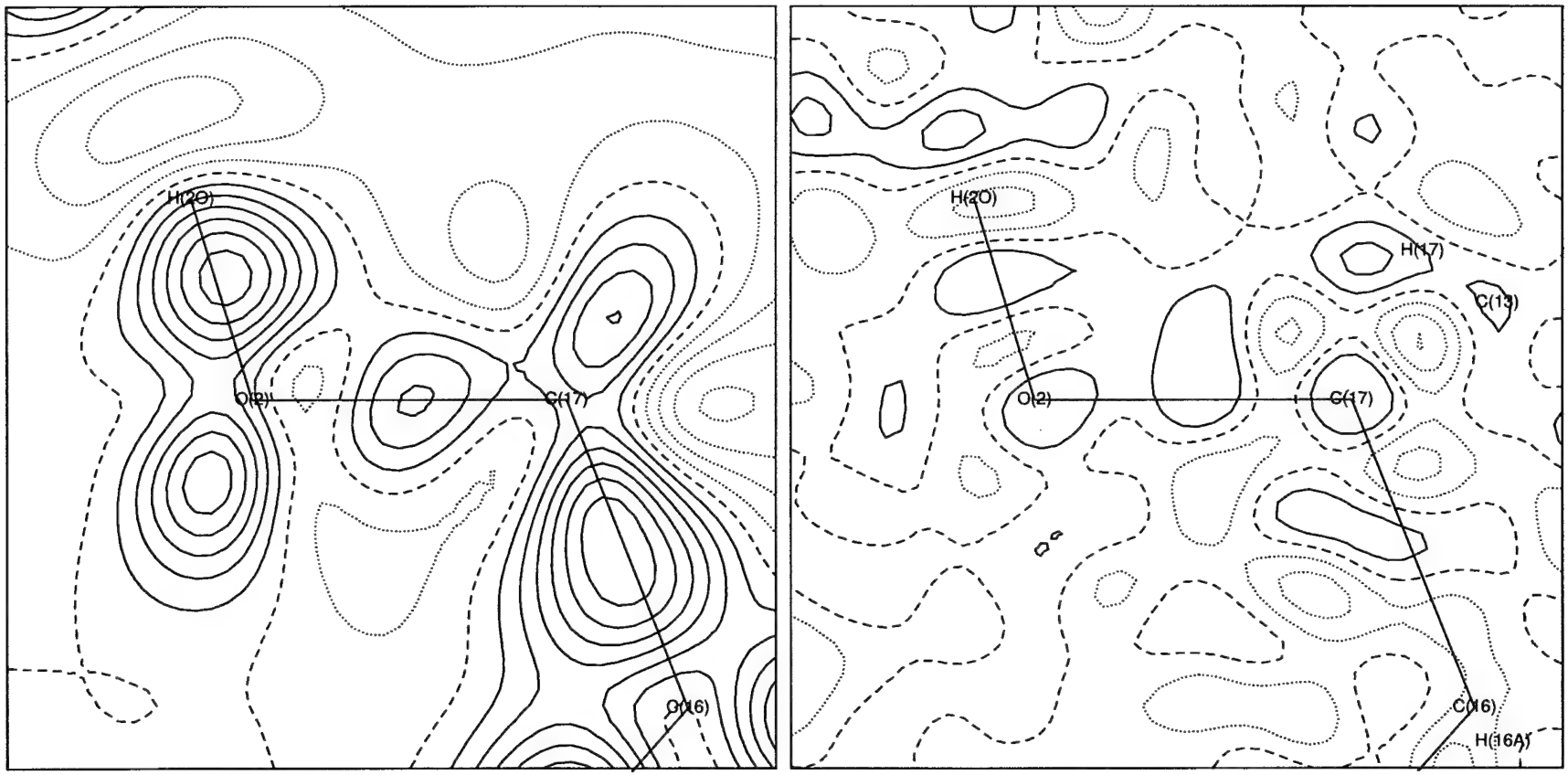

Figure 12. Dynamic model map and residual map in the C17 – O2 – H2O plane of 17β-estradiol•urea. Contour intervals are 0.05 eÅ^{-3} with solid lines positive, dashed lines zero, and dotted lines negative.

Figure 13. Dynamic model map and residual map in the plane of the lone pairs of O2 of 17β-estradiol•urea. Contour intervals are 0.05 eÅ^{-3} with solid lines positive, dashed lines zero, and dotted lines negative.

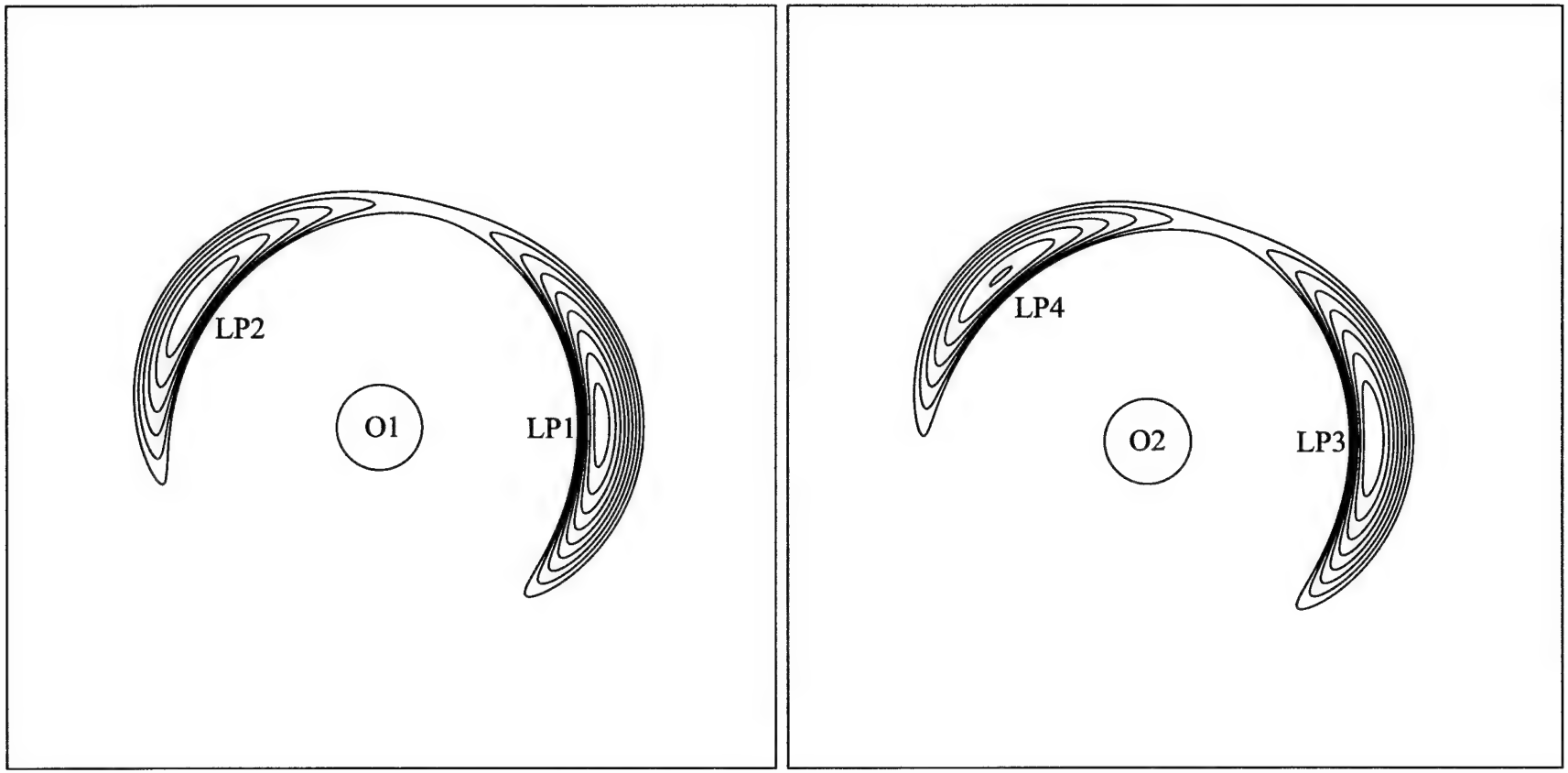

Figure 14. The Laplacian of the total electron density of atoms at rest in the plane of the lone pairs of the oxygen atoms of 17β-estradiol•urea. Contour intervals are 5 eÅ^{-5} starting at 90 eÅ^{-5} for O1 and 80 eÅ^{-5} for O2.

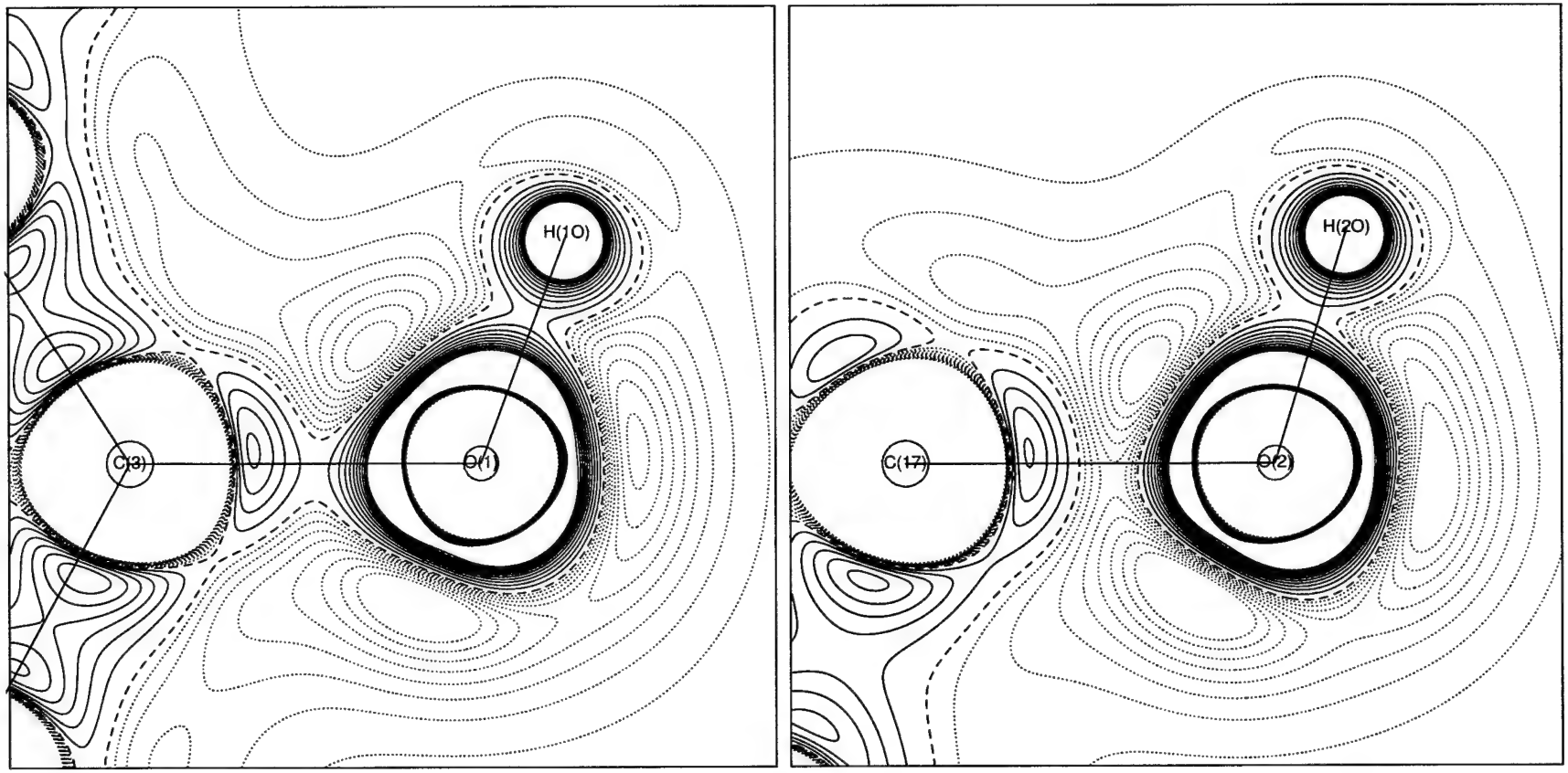

Figure 15. The Laplacian of the total electron density of atoms at rest in the C3–O1–H1O plane and C17–O2–H2O of 17β-estradiol•urea. Contour intervals are 5 eÅ^{-5} starting at 5 eÅ^{-5} (solid blue lines), -2 eÅ^{-5} starting at -2 eÅ^{-5} (dotted red lines), and the dashed line plots 0 eÅ^{-5}.

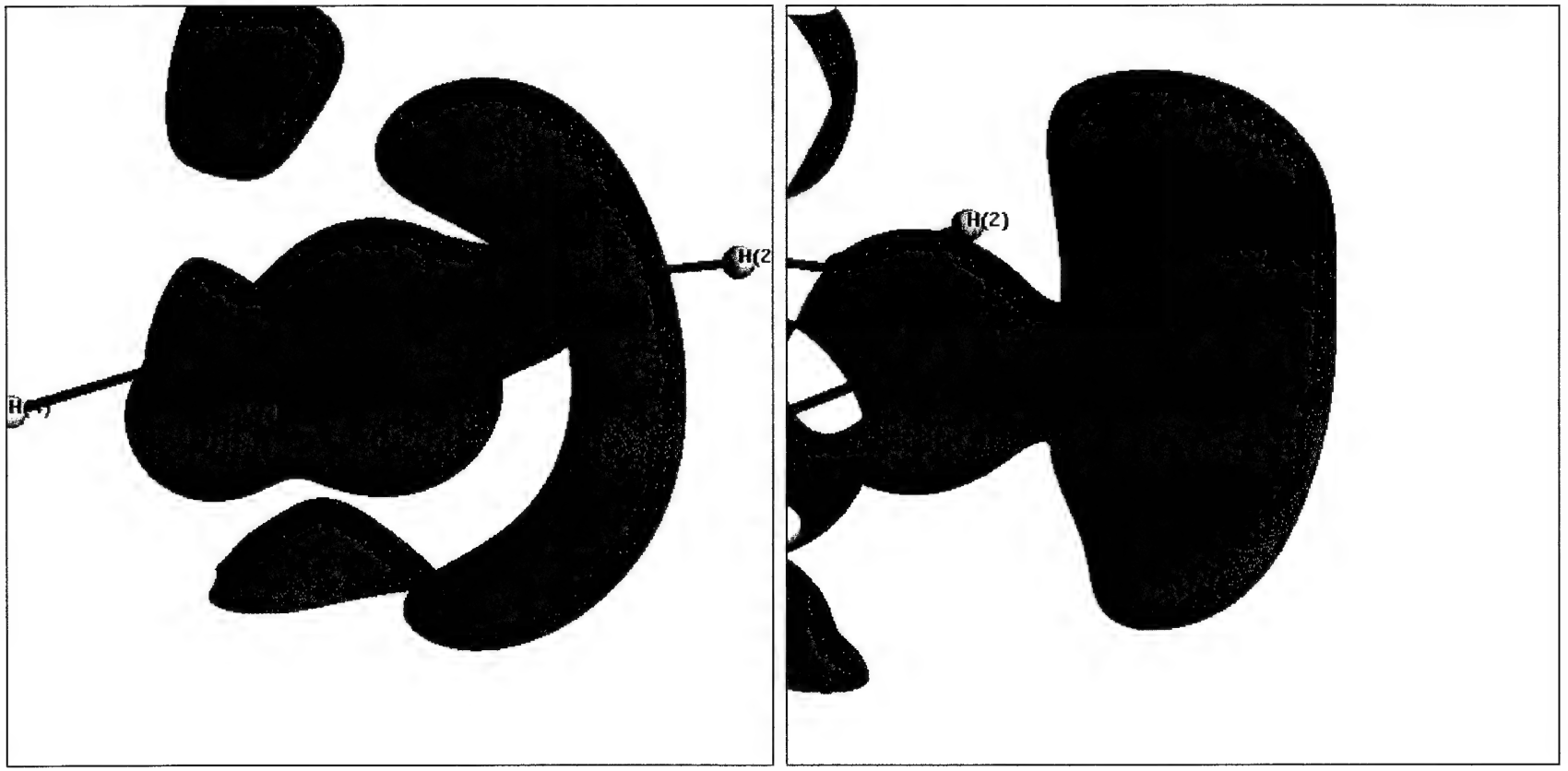

Figure 16. 17β-estradiol•urea, C3 hydroxy, red –0.15 eÅ^{-1}, blue 1.0 eÅ^{-1}.

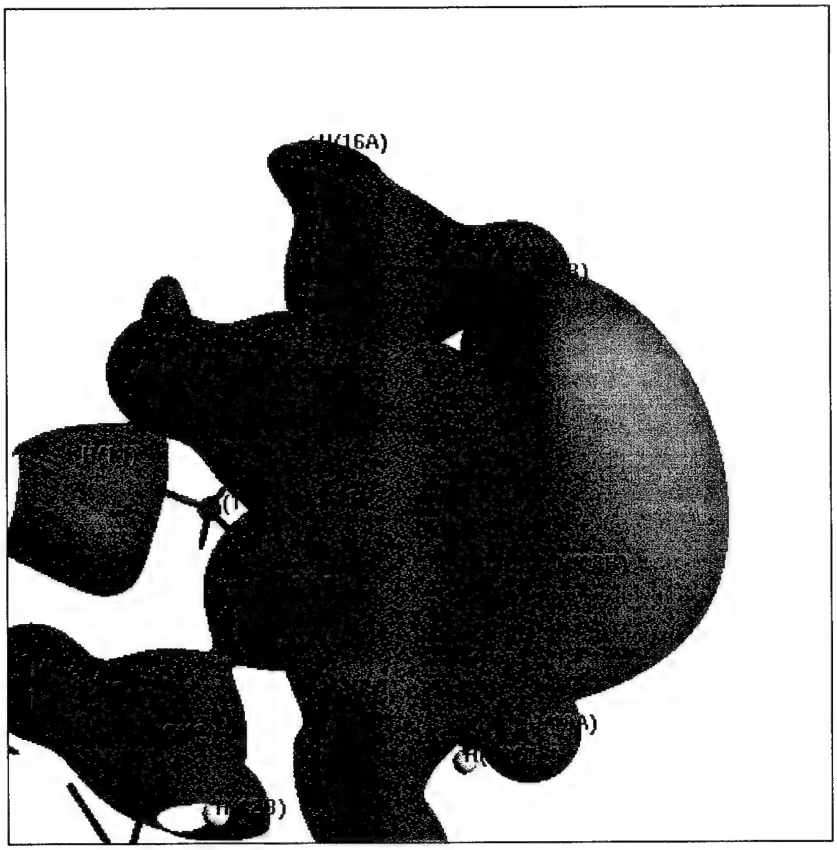

Figure 17. 17β-estradiol•urea, C17 hydroxy, red –0.15 eÅ^{-1}, blue 1.0 eÅ^{-1}.

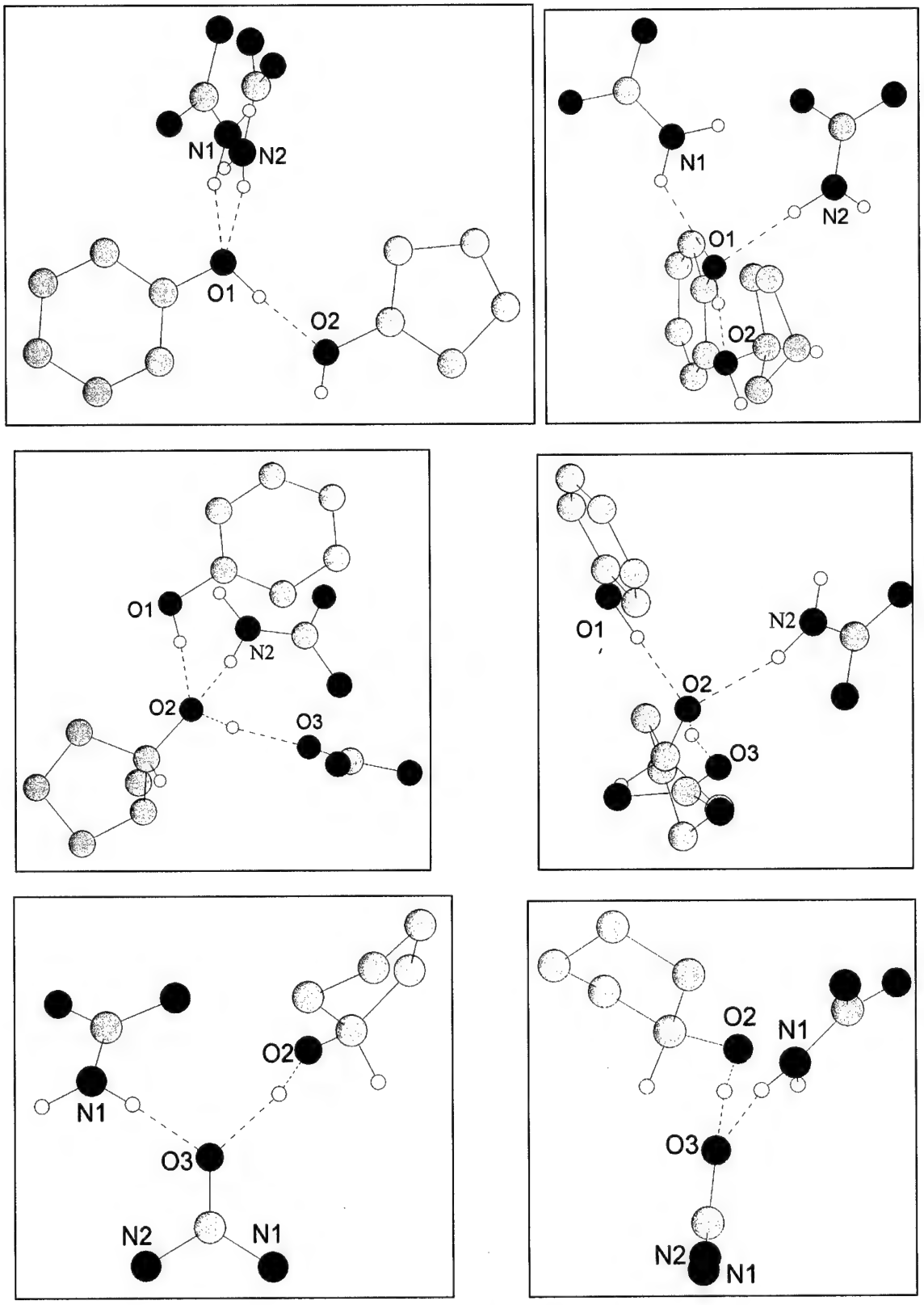

Figure 18. Geometry of hydrogen bonding interactions of 17β-estradiol•urea.

Appendix C.

17β-estradiol•½methanol

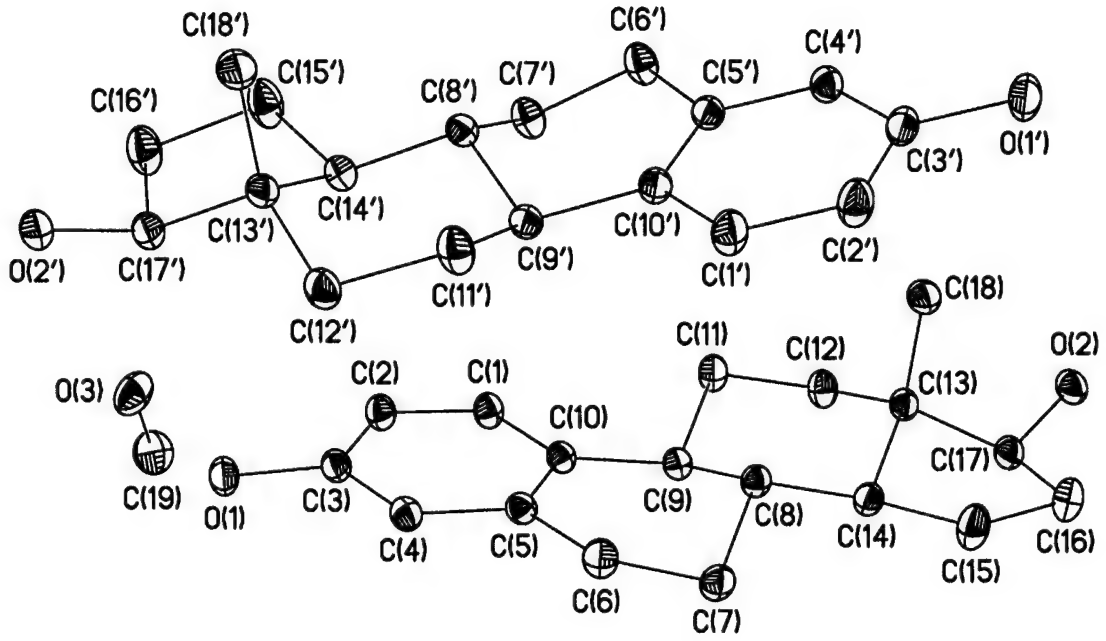

Figure 1. Thermal ellipsoid plot of 17β-estradiol•½methanol where ellipsoids represent 50% probability electron density of the atom. Hydrogen atoms are omitted for clarity.

Run	2θ	ω	ϕ	Scan Width (°)	# of Frames	Frame Times (sec)
1	-40	-46	22	-0.15	1100	16
2	-40	-46	112	-0.15	1100	16
3	-40	-46	202	-0.15	1100	16
4	-40	-46	292	-0.15	1100	16
5	-80	-86	67	-0.15	1100	32
6	-80	-86	157	-0.15	1100	32
7	-80	-86	247	-0.15	1100	32
8	-80	-86	337	-0.15	1100	32
9	-102	-108	22	-0.15	1100	64
10	-102	-108	112	-0.15	1100	64
11	-102	-108	202	-0.15	1100	64
12	-102	-108	292	-0.15	1100	64

Table 1. Data collection parameters for 17β-estradiol•½methanol.

Crystal Data			
Chemical Formula	$C_{37}H_{52}O_5$		
Temperature	100.0(1) K		
Crystal Dimensions	0.22 x 0.26 x 0.42 mm		
Space Group	P1		
A	7.2910(1) Å		
B	9.2768(1) Å		
C	12.3873(2) Å		
α	89.4704(6)		
β	87.8577(6)		
γ	70.7607(7)		
Volume	790.489(33) $Å^3$		
Z (Crystallographic)	2		
Integration Parameters			
	Box Size (°)	Profile Fitting (I/σ)	Simple Sum Perimeter Limit
Low Angle	1.5 x 1.5 x 1.0	20 20	0.02
Medium Angle	1.2 x 1.2 x 0.8	20 20	0.02
High Angle	1.0 x 1.0 x 0.6	10 10	0.02
Reflection Statistics (from SORTAV)			
Total Reflections	86369		
Rejected Outliers	33		
Unique Reflections	29051		
Average Redundancy	3.0		
Resolution	1.329 $Å^{-1}$		
Completeness	91.9 %		
R_1	5.77 %		
R_2	5.34 %		
R_w	15.25 %		
Z (Refinement)	1.219		

Table 2. Selected crystal, integration, and reflection data for 17β-estradiol•½methanol.

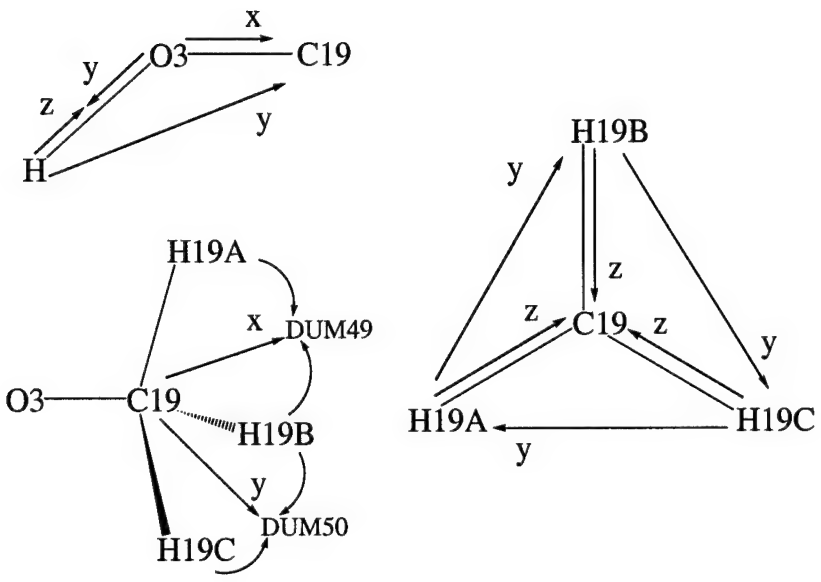

Figure 2. Coordinate system for the methanol molecule.

	n	m	$\langle n \rangle$	R_1	R_2	R_w	Z	V
Q < -4	0	0	0.0	0.0000	0.0000	0.0000	0.000	0.000
-4 < Q < -3	0	0	0.0	0.0000	0.0000	0.0000	0.000	0.000
-3 < Q < -2	8	4	2.0	0.3321	0.3844	0.3018	1.034	0.263
-2 < Q < -1	173	74	2.3	0.5492	0.6949	0.3870	0.761	0.455
-1 < Q < 0	2508	941	2.7	1.1243	1.1755	1.0245	1.183	2.153
0 < Q < 1	7959	2832	2.8	1.0254	1.0485	0.9274	1.329	1.501
1 < Q < 2	7845	2724	2.9	0.5759	0.6902	0.4618	1.252	0.519
2 < Q < 3	6736	2209	3.0	0.3661	0.4556	0.2863	1.194	0.322
3 < Q < 4	5725	1806	3.2	0.2602	0.3270	0.2132	1.220	0.235
4 < Q < 6	10058	2909	3.5	0.1800	0.2248	0.1548	1.231	0.170
6 < Q < 8	8497	2264	3.8	0.1266	0.1558	0.1169	1.254	0.127
8 < Q < 10	6921	1723	4.0	*0.0969*	0.1194	0.0927	1.242	0.101
10 < Q < 20	18395	4459	4.1	0.0596	0.0679	0.0645	1.224	0.063
20 < Q < 30	4702	1214	3.9	0.0389	0.0677	0.0370	1.193	0.040
30 < Q < 50	1174	361	3.3	0.0232	0.0273	0.0241	1.141	0.025
50 < Q < 100	212	75	2.8	0.0115	0.0136	0.0142	1.028	0.011
100 < Q	0	0	0.0	0.0000	0.0000	0.0000	0.000	0.000

Table 3. Intensity-Significance Intervals where n is the number of reflections, m is the number of unique reflections, $\langle n \rangle$ is the average measurement multiplicity, and Q=I/Max ($\sigma_{int}/\sigma_{ext}$) respectively for 17$\beta$-estradiol•½methanol.

	n	m	$\langle n \rangle$	R_1	R_2	R_w	Z	V
D > 1.016	4805	1570	3.1	.0345	.0529	.0721	1.568	.035
1.016 > D > 0.806	6705	1582	4.2	.0512	.0579	.0943	1.358	.057
0.806 > D > 0.705	6464	1594	4.1	.0554	.0578	.1004	1.337	.061
0.705 > D > 0.640	7744	1576	4.9	.0711	.0719	.1065	1.271	.075
0.640 > D > 0.594	8049	1558	5.2	.0792	.0777	.1080	1.250	.081
0.594 > D > 0.559	7545	1532	4.9	.1092	.1085	.1249	1.189	.105
0.559 > D > 0.531	6152	1521	4.0	.1373	.1371	.1424	1.155	.124
.531 > D > 0.508	4376	1441	3.0	.1334	.1241	.1677	1.274	.135
.508 > D > 0.488	4098	1401	2.9	.1508	.1428	.1755	1.245	.148
.488 > D > 0.472	4118	1436	2.9	.1593	.1445	.1895	1.280	.155
.472 > D > 0.457	3747	1354	2.8	.1854	.1681	.1988	1.230	.177
.457 > D > 0.444	3746	1387	2.7	.2289	.2205	.2122	1.192	.215
.444 > D > 0.432	3456	1331	2.6	.3003	.3007	.2497	1.183	.270
.432 > D > 0.422	3298	1303	2.5	.3737	.3823	.2719	1.167	.333
.422 > D > 0.412	2886	1194	2.4	.3703	.3773	.2801	1.166	.321
.412 > D > 0.403	1376	641	2.1	.3296	.3234	.3198	1.396	.309
.403 > D > 0.395	986	493	2.0	.3404	.3040	.3670	1.502	.352
.395 > D > 0.388	754	377	2.0	.4069	.3446	.4136	1.574	.431
.388 > D > 0.381	500	250	2.0	.4569	.4011	.4303	1.430	.486
.381 > D > 0.374	108	54	2.0	.5333	.4996	.5168	1.417	.584

Table 4. Equal-Volume Resolution Shells where n is the number of reflections, m is the number of unique reflections, $\langle n \rangle$ is the average measurement multiplicity, and S=sinθ/λ (Å^{-1}) respectively for 17β-estradiol•½methanol.

	Monopole	sp^2		sp^3
		20	33+	32-
O1	-0.50			
O2	-0.49			
C1	-0.30	-0.22	0.34	
C2	-0.38	-0.19	0.37	
C3	0.27	-0.21	0.38	
C4	-0.33	-0.17	0.36	
C5	-0.18	-0.22	0.33	
C6	-0.26			0.31
C7	-0.31			0.34
C8	-0.21			0.39
C9	-0.17			0.31
C10	-0.25	-0.18	0.37	
C11	-0.31			0.35
C12	-0.28			0.31
C13	-0.16			0.38
C14	-0.20			0.38
C15	-0.26			0.33
C16	-0.35			0.42
C17	0.20			0.38
C18	-0.32			0.27

	Monopole
H1O	0.40
H2O	0.38
H1	0.23
H2	0.22
H4	0.26
H6x	0.20
H7x	0.17
H8	0.20
H9	0.16
H11x	0.17
H12x	0.16
H14	0.19
H15x	0.16
H16x	0.18
H17	0.13
H18x	0.18

Atoms	Kappa	κ	κ'
O1, O2, O3	1	0.97	1.16
C3	2	1.01	0.92
C17	3	1.02	0.95
C1, C2, C4	4	0.97	0.92
C5, C10	5	0.98	0.87
C6, C7, C8, C9, C11, C12, C13, C14, C15, C16, C17, C18, C19	6	0.98	0.95
all C-H hydrogen atoms	7	1.20	1.29
H1O, H2O, H3O	8	1.20	1.29

Table 5. Starting values entered into the model for the multipole refinement for 17β-estradiol•½methanol. Units for multipole populations are e^-.

Atom	X	Y	Z
O1	0.08240(13)	0.21162(10)	0.936405(8)
O2	0.10594(13)	-0.05126(10)	0.06557(7)
C1	-0.06613(13)	0.15097(10)	0.66487(7)
C2	-0.08242(13)	0.19541(10)	0.77285(7)
C3	0.08629(14)	0.17723(11)	0.82894(7)
C4	0.26644(14)	0.12231(11)	0.77447(7)
C5	0.28180(13)	0.08148(10)	0.66531(7)
C6	0.48051(13)	0.03222(10)	0.60930(8)
C7	0.49100(12)	-0.05741(10)	0.50539(7)
C8	0.32007(13)	0.02383(10)	0.43507(7)
C9	0.12862(13)	0.02870(10)	0.49496(7)
C10	0.11375(14)	0.09174(11)	0.60917(7)
C11	-0.04837(13)	0.10675(10)	0.42644(7)
C12	-0.03113(14)	0.03067(11)	0.31502(7)
C13	0.15891(13)	0.02225(10)	0.25505(6)
C14	0.33043(13)	-0.05715(10)	0.32756(7)
C15	0.51074(13)	-0.08784(11)	0.25121(7)
C16	0.43778(12)	-0.11963(10)	0.14061(7)
C17	0.21795(13)	-0.09091(10)	0.15990(8)
C18	0.15271(14)	0.18231(10)	0.21808(7)

Atom	X	Y	Z
H1O	-0.0503(22)	0.2510(18)	0.9652(12)
H2O	0.1284(24)	0.0361(18)	0.0311(12)
H1	-0.2009(20)	0.1644(16)	0.6260(11)
H2	-0.2242(21)	0.2411(16)	0.8125(11)
H4	0.3944(20)	0.1116(16)	0.8194(10)
H6A	0.5897(19)	-0.0323(15)	0.6651(11)
H6B	0.5127(20)	0.1370(16)	0.5919(11)
H7A	0.4844(20)	-0.1709(16)	0.5233(11)
H7B	0.6269(20)	-0.0687(15)	0.4609(11)
H8	0.3190(21)	0.1410(16)	0.4195(11)
H9	0.1338(19)	-0.0908(15)	0.5028(10)
H11A	-0.1825(20)	0.1042(16)	0.4670(11)
H11B	-0.0617(20)	0.2269(16)	0.4192(11)
H12A	-0.0363(20)	-0.0845(16)	0.3270(11)
H12B	-0.1555(20)	0.0952(15)	0.2685(11)
H14	0.3164(20)	-0.1689(16)	0.3477(11)
H15A	0.6267(22)	-0.1869(17)	0.2797(12)
H15B	0.5532(22)	0.0144(17)	0.2507(12)
H16A	0.5101(21)	-0.2360(16)	0.1119(11)
H16B	0.4559(22)	-0.0401(17)	0.0791(12)
H17	0.1966(20)	-0.1975(15)	0.1875(11)
H18A	0.0354(21)	0.2267(16)	0.1658(11)
H18B	0.1336(20)	0.2577(16)	0.2845(11)
H18C	0.2817(22)	0.1811(17)	0.1751(12)

Table 6. Fractional atomic coordinates for molecule 1 of 17β-estradiol•½methanol.

Atom	X	Y	Z
O1'	0.44563(13)	0.49573(10)	0.14404(8)
O2'	0.15712(13)	0.64715(11)	1.02254(7)
C1'	0.50368(13)	0.44528(10)	0.43452(7)
C2'	0.54823(14)	0.44473(10)	0.32415(8)
C3'	0.39817(13)	0.49586(10)	0.25199(7)
C4'	0.20597(13)	0.54530(10)	0.29149(7)
C5'	0.16168(13)	0.54570(11)	0.40252(7)
C6'	-0.05026(14)	0.60488(10)	0.43907(7)
C7'	-0.08644(13)	0.56878(10)	0.55668(8)
C8'	0.06136(13)	0.60192(10)	0.62803(7)
C9'	0.26559(13)	0.49008(11)	0.59721(7)
C10'	0.31159(13)	0.49584(10)	0.47642(7)
C11'	0.42220(13)	0.51079(10)	0.66974(7)
C12'	0.37063(14)	0.50141(10)	0.79075(8)
C13'	0.17009(14)	0.61553(11)	0.82063(7)
C14'	0.01990(13)	0.58481(10)	0.74798(7)
C15'	-0.17643(13)	0.68090(10)	0.79979(7)
C16'	-0.13940(13)	0.66862(10)	0.92246(7)
C17'	0.08319(13)	0.59214(11)	0.93220(7)
C18'	0.17533(13)	0.77899(10)	0.81232(8)
O3	-0.28167(13)	0.29338(10)	1.01529(7)
C19	-0.35895(13)	0.17109(11)	1.02075(7)
H3O	-0.35307(25)	0.37300(22)	1.06225(17)
H19A	-0.29199(24)	0.08909(21)	0.95875(15)
H19B	-0.51182(24)	0.21209(20)	1.00791(15)
H19C	-0.34233(23)	0.11940(20)	1.09895(15)

Atom	X	Y	Z
H1O'	0.3341(22)	0.5447(17)	0.1007(12)
H2O'	0.1344 (23)	0.7561(17)	1.0186(12)
H1'	0.6239 (21)	0.4062(16)	0.4879(11)
H2'	0.6958(21)	0.4029(16)	0.2915(11)
H4'	0.0906(20)	0.5827(15)	0.2349(11)
H6C	-0.1306(20)	0.5579(15)	0.3848(11)
H6D	-0.1013(21)	0.7288(17)	0.4312(12)
H7C	-0.0741(20)	0.4489(16)	0.5651(11)
H7D	-0.2360(19)	0.6359(15)	0.5793(10)
H8'	0.0560(19)	0.7196(15)	0.6101(10)
H9'	0.2574(20)	0.3759(16)	0.6148(11)
H11C	0.5588(21)	0.4192(17)	0.6528(11)
H11D	0.4370(20)	0.6218(16)	0.6521(11)
H12C	0.3708 (21)	0.3860(16)	0.8082(11)
H12D	0.4841(20)	0.5202(16)	0.8379(11)
H14'	0.0331(20)	0.4644(16)	0.7608(11)
H15C	-0.2902(21)	0.6352(16)	0.7785(11)
H15D	-0.2110(22)	0.8005(17)	0.7772(12)
H16C	-0.2159(21)	0.6001(17)	0.9642(12)
H16D	-0.1856(22)	0.7791(17)	0.9632(13)
H17'	0.1173(20)	0.4698(15)	0.9497(10)
H18D	0.2891(21)	0.7876(16)	0.8599(11)
H18E	0.2046(20)	0.8088(16)	0.7323(11)
H18F	0.0440(23)	0.8618(18)	0.8405(12)

Table 7. Fractional atomic coordinates for molecule 2 and methanol of 17β-estradiol•½methanol.

Atom	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.02315(12)	0.01838(11)	0.01172(8)	-0.00821(9)	0.00038(8)	-0.00143(7)
O2	0.02742(14)	0.01660(10)	0.01237(8)	-0.00827(10)	-0.00257(8)	-0.00055(7)
C1	0.01183(10)	0.02079(13)	0.01240(9)	-0.00540(9)	0.00016(8)	-0.00046(9)
C2	0.01489(11)	0.01999(13)	0.01241(10)	-0.00567(10)	0.00116(8)	-0.00063(9)
C3	0.01715(12)	0.01344(10)	0.01130(9)	-0.00612(9)	-0.00016(8)	0.00036(8)
C4	0.01523(11)	0.01497(11)	0.01220(9)	-0.00595(9)	-0.00180(8)	0.00039(8)
C5	0.01212(10)	0.01365(10)	0.01193(9)	-0.00438(8)	-0.00169(8)	0.00091(8)
C6	0.01108(10)	0.02189(14)	0.01563(11)	-0.00391(10)	-0.00226(8)	-0.00091(10)
C7	0.01153(10)	0.01874(13)	0.01690(11)	-0.00068(9)	-0.00173(9)	-0.00146(10)
C8	0.01108(9)	0.01379(10)	0.01239(9)	-0.00381(8)	-0.00023(7)	-0.00045(8)
C9	0.01150(10)	0.01434(11)	0.01169(9)	-0.00501(8)	-0.00072(7)	0.00044(8)
C10	0.01091(9)	0.01456(11)	0.01085(9)	-0.00475(8)	-0.00064(7)	0.00068(8)
C11	0.01118(10)	0.02348(15)	0.01289(10)	-0.00428(10)	-0.00113(8)	-0.00183(9)
C12	0.01433(11)	0.02257(15)	0.01333(10)	-0.00799(10)	-0.00128(8)	-0.00153(9)
C13	0.01540(11)	0.01279(10)	0.01145(9)	-0.00557(9)	-0.00003(8)	-0.00079(7)
C14	0.01351(10)	0.01445(11)	0.01285(9)	-0.00400(9)	0.00044(8)	-0.00125(8)
C15	0.01524(13)	0.02956(19)	0.01735(13)	-0.00556(13)	0.00290(10)	-0.00514(12)
C16	0.02131(15)	0.02492(17)	0.01594(12)	-0.00703(13)	0.00430(11)	-0.00569(11)
C17	0.02088(13)	0.01382(11)	0.01227(10)	-0.00648(15)	-0.00006(11)	-0.00162(13)
C18	0.02731(16)	0.01397(12)	0.01504(11)	-0.00815(11)	-0.00065(11)	0.00034(9)
O1'	0.02050(12)	0.02548(14)	0.01264(9)	-0.00112(10)	0.00182(8)	-0.00266(9)
O2'	0.02908(14)	0.01675(10)	0.01253(8)	-0.00712(10)	-0.00434(9)	-0.00013(7)
C1'	0.01201(11)	0.02698(17)	0.01402(11)	0.00007(11)	-0.00084(13)	-0.00137(10)
C2'	0.01366(12)	0.02877(18)	0.01463(11)	-0.00027(11)	0.00023(9)	-0.00244(11)
C3'	0.01544(12)	0.01728(12)	0.01231(10)	-0.00199(10)	0.00038(9)	-0.00223(9)
C4'	0.01434(11)	0.01596(11)	0.01173(9)	-0.00340(9)	-0.00136(8)	-0.00047(8)
C5'	0.01218(10)	0.01417(10)	0.01179(9)	-0.00328(8)	-0.00185(8)	0.00034(8)
C6'	0.01206(11)	0.02589(16)	0.01333(10)	-0.00459(10)	-0.00254(8)	0.00307(10)
C7'	0.01301(11)	0.02461(15)	0.01363(10)	-0.00787(10)	-0.00229(8)	0.00273(10)
C8'	0.01167(9)	0.01277(10)	0.01186(9)	-0.00365(8)	-0.00136(7)	0.00172(7)
C9'	0.01227(10)	0.01343(10)	0.01241(9)	-0.00207(8)	-0.00242(8)	0.00063(8)
C10'	0.01146(10)	0.01537(11)	0.01218(9)	-0.00169(8)	-0.00187(8)	-0.00036(8)
C11'	0.01272(11)	0.02953(18)	0.01384(11)	-0.00590(12)	-0.00282(9)	0.00010(11)
C12'	0.01563(12)	0.02041(14)	0.01340(10)	-0.00364(11)	-0.00403(10)	0.00092(9)
C13'	0.01718(11)	0.01090(9)	0.01195(9)	-0.00572(9)	-0.00183(8)	0.00114(7)
C14'	0.01426(11)	0.01539(11)	0.01184(9)	-0.00583(9)	-0.00107(8)	0.00163(8)
C15'	0.01570(13)	0.03738(24)	0.01515(12)	-0.00321(14)	0.00057(10)	0.00073(13)
C16'	0.02051(15)	0.03456(22)	0.01457(12)	-0.00670(15)	0.00243(11)	-0.00056(13)
C17'	0.02185(14)	0.01486(11)	0.01165(9)	-0.00722(10)	-0.00124(9)	0.00096(8)
C18'	0.03705(22)	0.01437(12)	0.01709(12)	-0.01337(14)	-0.00299(13)	0.00180(10)
O3	0.02682(15)	0.02440(15)	0.02598(14)	-0.00745(12)	0.01130(12)	-0.00554(12)
C19	0.02730(20)	0.03127(23)	0.02636(19)	-0.01196(18)	0.00339(15)	0.00142(16)

Table 8. Anisotropic thermal parameters of non-H atoms for 17β-estradiol•½methanol.

Atom	U_{iso}
H1O	0.0320(26)
H2O	0.0353(29)
H1	0.0453(25)
H2	0.0460(26)
H4	0.0429(24)
H6A	0.0404(21)
H6B	0.0491(26)
H7A	0.0495(25)
H7B	0.0475(24)
H8	0.0457(24)
H9	0.0386(21)
H11A	0.0488(25)
H11B	0.0493(25)
H12A	0.0519(26)
H12B	0.0462(24)
H14	0.0414(22)
H15A	0.0601(29)
H15B	0.0558(28)
H16A	0.0592(28)
H16B	0.0602(29)
H17	0.0505(23)
H18A	0.0572(27)
H18B	0.0554(26)
H18C	0.0658(31)

Atom	U_{iso}
H1O'	0.0326(27)
H2O'	0.0316(26)
H1'	0.0470(24)
H2'	0.0495(26)
H4'	0.0393(22)
H6C	0.0478(24)
H6D	0.0580(29)
H7C	0.0512(26)
H7D	0.0428(22)
H8'	0.0422(23)
H9'	0.0479(25)
H11C	0.0550(28)
H11D	0.0519(26)
H12C	0.0515(26)
H12D	0.0505(25)
H14'	0.0450(23)
H15C	0.0578(29)
H15D	0.0600(30)
H16C	0.0636(31)
H16D	0.0657(31)
H17'	0.0553(24)
H18D	0.0590(28)
H18E	0.0611(29)
H18F	0.0749(36)

H3O	0.0402(30)
H19A	0.0770(36)
H19B	0.0837(40)
H19C	0.0903(43)

Table 9. Isotropic thermal parameters of H atoms for 17β-estradiol•½methanol.

Atoms	Bond Length (Å)
O1 – C3	1.3688(4)
O2 – C17	1.4259(5)
C1 – C2	1.3926(5)
C1 – C10	1.4009(4)
C2 – C3	1.3961(5)
C3 – C4	1.3925(5)
C4 – C5	1.3981(5)
C5 – C6	1.5111(5)
C5 – C10	1.4069(4)
C6 – C7	1.5247(5)
C7 – C8	1.5264(5)
C8 – C9	1.5435(4)
C8 – C14	1.5222(5)
C9 – C10	1.5223(5)
C9 – C11	1.5377(5)
C11 – C12	1.5381(5)
C12 – C13	1.5266(5)
C13 – C14	1.5421(5)
C13 – C17	1.5374(5)
C13 – C18	1.5366(5)
C14 – C15	1.5392(5)
C15 – C16	1.5532(6)
C16 – C17	1.5453(6)

Atoms	Bond Length (Å)
O1' – C3'	1.3687(4)
O2' – C17'	1.4284(5)
C1' – C2'	1.3930(5)
C1' – C10'	1.4029(5)
C2' – C3'	1.3944(5)
C3' – C4'	1.3938(5)
C4' – C5'	1.4007(4)
C5' – C6'	1.5124(5)
C5' – C10'	1.4073(4)
C6' – C7'	1.5247(5)
C7' – C8'	1.5270(5)
C8' – C9'	1.5447(4)
C8' – C14'	1.5225(4)
C9' – C10'	1.5254(4)
C9' – C11'	1.5404(5)
C11' – C12'	1.5405(5)
C12' – C13'	1.5304(5)
C13' – C14'	1.5408(5)
C13' – C17'	1.5421(5)
C13' – C18'	1.5319(5)
C14' – C15'	1.5351(5)
C15' – C16'	1.5499(6)
C16' – C17'	1.5511(6)

O3 – C19	1.4234(8)

Table 10. Bond distances of non-H atoms of 17β-estradiol•½methanol.

Atoms	Bond Angle (°)
C3 – O1 – H1O	110.8(8)
C17 – O2 – H2O	109.5(8)
C2 – C1 – C10	122.4(1)
C2 – C1 – H1	116.1(6)
C10 – C1 – H1	121.4(6)
C1 – C2 – C3	119.1(1)
C1 – C2 – H2	119.9(6)
C3 – C2 – H2	120.9(6)
O1 – C3 – C2	122.5(1)
O1 – C3 – C4	118.1(1)
C2 – C3 – C4	119.4(1)
C3 – C4 – C5	121.2(1)
C3 – C4 – H4	117.9(6)
C5 – C4 – H4	120.9(6)
C4 – C5 – C6	118.5(1)
C4 – C5 – C10	120.0(1)
C6 – C5 – C10	121.5(1)
C5 – C6 - C7	113.4(1)
C5 – C6 – H6A	109.9(6)
C5 – C6 – H6B	105.9(6)
C7 – C6 – H6A	111.1(6)
C7 – C6 – H6B	110.2(6)
H6A – C6 – H6B	106.1(9)
C6 – C7 – C8	110.5(1)
C6 – C7 – H7A	110.7(6)
C6 – C7 – H7B	109.5(6)
C8 – C7 – H7A	107.7(6)
C8 – C7 – H7B	109.4(6)
H7A – C7 – H7B	109.0(8)
C7 – C8 – C9	109.3(1)
C7 – C8 – C14	112.3(1)

Atoms	Bond Angle (°)
C9 – C8 – C14	107.7(1)
C7 – C8 – H8	109.1(6)
C9 – C8 – H8	109.5(6)
C14 – C8 – H8	108.9(6)
C8 – C9 – C10	112.1(1)
C8 – C9 – C11	111.4(1)
C10 – C9 – C11	114.5(1)
C8 – C9 – H9	106.0(6)
C10 – C9 – H9	106.7(6)
C11 – C9 – H9	105.4(6)
C1 – C10 – C5	117.7(1)
C1 – C10 – C9	121.2(1)
C5 – C10 – C9	120.9(1)
C9 – C11 – C12	112.0(1)
C9 – C11 – H11A	111.2(6)
C9 – C11 – H11B	107.7(6)
C12 – C11 – H11A	108.2(6)
C12 – C11 – H11B	111.5(6)
H11A – C11 – H11B	106.0(8)
C11 – C12 – C13	111.5(1)
C11 – C12 – H12A	108.2(6)
C11 – C12 – H12B	108.6(6)
C13 – C12 – H12A	109.3(6)
C13 – C12 – H12B	110.7(6)
H12A – C12 – H12B	108.5(9)
C12 – C13 – C14	109.1(1)
C12 – C13 – C17	115.2(1)
C12 – C13 – C18	110.2(1)
C14 – C13 – C17	97.9(1)
C14 – C13 – C18	113.5(1)
C17 – C13 – C18	110.5(1)

Atoms	Bond Angle (°)
C8 – C14 – C13	113.4(1)
C8 – C14 – C15	120.3(1)
C13 – C14 – C15	103.9(1)
C8 – C14 – H14	105.8(6)
C13 – C14 – H14	105.6(6)
C15 – C14 – H14	106.8(6)
C14 – C15 – C16	103.6(1)
C14 – C15 – H15A	109.4(6)
C14 – C15 – H15B	107.5(6)
C16 – C15 – H15A	111.6(6)
C16 – C15 – H15B	112.9(6)
H15A – C15 – H15B	111.4(10)
C15 – C16 – C17	105.2(1)
C15 – C16 – H16A	112.9(6)
C15 – C16 – H16B	111.3(6)
C17 – C16 – H16A	110.1(6)
C17 – C16 – H16B	108.3(6)
H16A – C16 – H16B	109.0(9)
O2 – C17 – C13	117.1(1)
O2 – C17 – C16	114.7(1)
C13 – C17 – C16	104.4(1)
O2 – C17 – H17	104.1(6)
C13 – C17 – H17	107.2(6)
C16 – C17 – H17	109.0(6)
C13 – C18 – H18A	108.9(7)
C13 – C18 – H18B	111.6(6)
C13 – C18 – H18C	112.4(7)
H18A – C18 – H18B	109.0(9)
H18A – C18 – H18C	107.7(9)
H18B – C18 – H18C	107.1(10)

Table 11. Bond angles for molecule 1 of 17β-estradiol•½methanol.

Atoms	Bond Angle (°)
C3' – O1' – H1O'	112.9(8)
C17' – O2' – H2O'	112.3(8)
C2' – C1' – C10'	122.2(1)
C2' – C1' – H1'	117.3(6)
C10' – C1' – H1'	120.4(6)
C1' – C2' – C3'	119.5(1)
C1' – C2' – H2'	122.4(6)
C3' – C2' – H2'	118.1(6)
O1' – C3' – C2'	118.4(1)
O1' – C3' – C4'	122.2(1)
C2' – C3' – C4'	119.4(1)
C3' – C4' – C5'	121.0(1)
C3' – C4' – H4'	118.9(6)
C5' – C4' – H4'	120.1(6)
C4' – C5' – C6'	117.7(1)
C4' – C5' – C10'	120.3(1)
C6' – C5' – C10'	122.0(1)
C5' – C6' – C7'	113.6(1)
C5' – C6' – H6C	107.7(6)
C5' – C6' – H6D	108.1(6)
C7' – C6' – H6C	111.4(6)
C7' – C6' – H6D	107.2(6)
H6C – C6' – H6D	108.7(9)
C6' – C7' – C8'	110.3(1)
C6' – C7' – H7C	110.3(6)
C6' – C7' – H7D	107.5(6)
C8' – C7' – H7C	108.9(6)
C8' – C7' – H7D	112.8(6)
H7C – C7' – H7D	107.1(8)
C7' – C8' – C9'	108.7(1)
C7' – C8' – C14'	112.9(1)
C9' – C8' – C14'	108.7(1)
C7' – C8' – H8'	106.6(6)

Atoms	Bond Angle (°)
C'9 – C8' – H8'	109.6(6)
C14' – C8' – H8'	110.3(6)
C8' – C9' – C10'	111.2(1)
C8' – C9' – C11'	111.9(1)
C10' – C9' – C11'	114.2(1)
C8' – C9' – H9'	105.1(6)
C10' – C9' – H9'	107.3(6)
C11' – C9' – H9'	106.4(6)
C1' – C10' – C5'	117.6(1)
C1' – C10' – C9'	121.4(1)
C5' – C10' – C9'	120.9(1)
C9' – C11' – C12'	112.2(1)
C9' – C11' – H11C	109.0(6)
C9' – C11' – H11D	108.1(6)
C12' – C11' – H11C	107.0(6)
C12' – C11' – H11D	109.7(6)
H11C – C11' – H11D	110.9(9)
C11' – C12' – C13'	111.1(1)
C11' – C12' – H12C	108.4(6)
C11' – C12' – H12D	108.9(6)
C13' – C12' – H12C	109.4(6)
C13' – C12' – H12D	111.8(6)
H12C – C12' – H12D	107.1(9)
C12' – C13' – C14'	108.4(1)
C12' – C13' – C17'	115.6(1)
C12' – C13' – C18'	110.1(1)
C14' – C13' – C17'	99.4(1)
C14' – C13' – C18'	113.5(1)
C17' – C13' – C18'	109.6(1)
C8' – C14' – C13'	113.3(1)
C8' – C14' – C15'	119.6(1)
C13' – C14' – C15'	103.7(1)
C8' – C14' – H14'	106.6(6)

Atoms	Bond Angle (°)
C13' – C14' – H14'	105.9(6)
C15' – C14' – H14'	106.8(6)
C14' – C15' – C16'	103.5(1)
C14' – C15' – H15C	110.5(6)
C14' – C15' – H15D	110.5(6)
C16' – C15' – H15C	112.2(6)
C16' – C15' – H15D	107.6(6)
H15C – C15' – H15D	112.1(9)
C15' – C16' – C17'	106.0(1)
C15' – C16' – H16C	112.1(6)
C15' – C16' – H16D	113.1(6)
C17' – C16' – H16C	110.0(6)
C17' – C16' – H16D	109.3(6)
H16C – C16' – H16D	106.4(10)
O2' – C17' – C13'	115.7(1)
O2' – C17' – C16'	112.8(1)
C13' – C17' – C16'	104.6(1)
O2' – C17' – H17'	103.2(6)
C13' – C17' – H17'	110.7(6)
C16' – C17' – H17'	109.9(6)
C13' – C18' – H18D	108.4(7)
C13' – C18' – H18E	112.6(7)
C13' – C18' – H18F	112.9(8)
H18D – C18' – H18E	107.1(9)
H18D – C18' – H18F	108.1(10)
H18E – C18' – H18F	107.6(10)
C19 – O3 – H3O	110.4(9)
O3 – C19 – H19A	110.0(5)
O3 – C19 – H19B	110.5(5)
O3 – C19 – H19C	111.3(5)
H19A – C19 – H19B	107.4(8)
H19A – C19 – H19C	111.3(8)
H19B – C19 – H19C	106.1(8)

Table 12. Bond angles for molecule 2 and methanol of 17β-estradiol•½methanol.

Atom	Monopole Population ($P_{0,0}$)
O1	6.536(20)
O2	6.533(20)
C1	4.200(34)
C2	4.241(36)
C3	3.857(34)
C4	4.279(36)
C5	4.107(32)
C6	4.216(37)
C7	4.211(37)
C8	4.124(36)
C9	4.101(35)
C10	4.123(36)
C11	4.205(36)
C12	4.187(37)
C13	4.232(32)
C14	4.131(33)
C15	4.313(37)
C16	4.366(36)
C17	3.874(34)
C18	4.355(37)
O3	6.491(20)
C19	4.264(35)

Atom	Monopole Population ($P_{0,0}$)
O1'	6.539(21)
O2'	6.543(21)
C1'	4.194(36)
C2'	4.256(35)
C3'	3.875(34)
C4'	4.295(34)
C5'	4.123(34)
C6'	4.222(35)
C7'	4.199(34)
C8'	4.115(35)
C9'	4.115(33)
C10'	4.090(35)
C11'	4.215(36)
C12'	4.215(36)
C13'	4.220(34)
C14'	4.120(35)
C15'	4.309(37)
C16'	4.344(37)
C17'	3.852(33)
C18'	4.365(36)

Table 13. Monopole populations (e^-) of non-H atoms of 17β-estradiol•½methanol.

Atom	Monopole Population ($P_{0,0}$)
H1O	0.665(19)
H2O	0.636(19)
H1	0.783(19)
H2	0.769(19)
H4	0.776(19)
H6A	0.826(14)
H6B	0.826(14)
H7A	0.842(14)
H7B	0.842(14)
H8	0.819(19)
H9	0.833(17)
H11A	0.833(14)
H11B	0.833(14)
H12A	0.837(14)
H12B	0.837(14)
H14	0.820(18)
H15A	0.857(15)
H15B	0.857(15)
H16A	0.872(14)
H16B	0.872(14)
H17	0.916(20)
H18A	0.887(13)
H18B	0.887(13)
H18C	0.887(13)
H3O	0.696(20)
H19A	0.850(12)
H19B	0.850(12)
H19C	0.850(12)

Atom	Monopole Population ($P_{0,0}$)
H1O'	0.638(18)
H2O'	0.651(18)
H1'	0.796(19)
H2'	0.788(21)
H4'	0.790(19)
H6C	0.832(15)
H6D	0.832(15)
H7C	0.842(14)
H7D	0.842(14)
H8'	0.803(18)
H9'	0.829(20)
H11C	0.827(15)
H11D	0.827(15)
H12C	0.841(14)
H12D	0.841(14)
H14'	0.821(19)
H15C	0.841(15)
H15D	0.841(15)
H16C	0.870(15)
H16D	0.870(15)
H17'	0.939(20)
H18D	0.879(13)
H18E	0.879(13)
H18F	0.879(13)

Table 14. Monopole populations (e^-) of H atoms of 17β-estradiol•½methanol.

Multipoles	O1	O1'	O2	O2'	O3
$P_{1,+1}$	-0.025(17)	-0.033(17)	-0.043(17)	-0.028(18)	-0.046(20)
$P_{1,-1}$	0.030(19)	0.0	0.0	0.0	0.0
$P_{1,0}$	0.0	0.0	0.0	0.0	-0.068(19)
$P_{2,0}$	0.117(12)	0.127(13)	0.083(12)	0.089(12)	0.063(14)
$P_{2,+1}$	-0.033(11)	-0.016(12)	-0.021(11)	-0.018(11)	-0.038(14)
$P_{2,-1}$	-0.047(11)	-0.027(12)	0.0	-0.021(12)	-0.014(13)
$P_{2,+2}$	-0.042(11)	-0.035(11)	-0.077(11)	-0.046(11)	0.0
$P_{2,-2}$	-0.017(11)	0.0	0.0	0.0	0.0
$P_{3,0}$	-0.029(20)	0.0	0.0	0.050(22)	-0.040(25)
$P_{3,+1}$	-0.029(19)	0.0	0.0	0.0	-0.026(24)
$P_{3,-1}$	-0.028(20)	0.0	-0.024(20)	0.0	0.027(21)
$P_{3,+2}$	0.0	0.0	0.0	0.0	0.0
$P_{3,-2}$	0.0	0.034(21)	0.0	0.0	0.0
$P_{3,+3}$	0.083(18)	0.095(18)	0.075(19)	0.102(19)	0.073(20)
$P_{3,-3}$	-0.019(19)	0.0	0.0	-0.038(19)	-0.037(21)
$P_{4,0}$	0.037(19)	0.057(22)	0.0	0.025(20)	0.0
$P_{4,+1}$	0.0	-0.035(20)	0.0	0.0	0.0
$P_{4,-1}$	0.053(18)	0.0	0.025(18)	0.040(18)	0.0
$P_{4,+2}$	0.0	0.0	0.0	0.023(19)	0.023(22)
$P_{4,-2}$	0.0	0.0	0.0	0.021(19)	0.067(23)
$P_{4,+3}$	0.0	0.0	-0.039(18)	0.0	0.0
$P_{4,-3}$	0.0	-0.022(18)	0.020(18)	0.0	0.0
$P_{4,+4}$	0.024(16)	0.038(16)	0.0	0.0	0.020(18)
$P_{4,-4}$	0.0	0.036(17)	0.0	-0.020(16)	-0.030(20)

Table 15. Multipole populations (e^-) of Oxygen atoms of 17β-estradiol•½methanol.

Multipoles	C1	C1'	C2	C2'	C3	C3'	C4	C4'	C5	C5'
$P_{1,+1}$	0.031(29)	0.051(29)	0.0	0.125(29)	0.0	0.082(23)	-0.056(28)	-0.036(28)	0.037(31)	0.0
$P_{1,-1}$	0.0	0.129(31)	-0.040(28)	0.0	0.080(22)	0.0	0.0	0.0	0.087(28)	-0.029(29)
$P_{1,0}$	0.0	0.032(29)	0.0	-0.049(29)	0.032(21)	-0.031(23)	0.0	0.0	0.0	-0.027(27)
$P_{2,0}$	-0.154(19)	-0.150(21)	-0.178(19)	-0.147(21)	-0.118(15)	-0.122(16)	-0.142(18)	-0.176(19)	-0.198(18)	-0.127(18)
$P_{2,+1}$	0.060(19)	0.045(20)	0.044(19)	0.0	-0.031(15)	-0.037(16)	-0.025(18)	0.0	-0.026(18)	0.065(18)
$P_{2,-1}$	0.029(19)	0.0	0.0	0.0	-0.018(15)	0.0	-0.068(18)	0.026(18)	0.027(18)	0.0
$P_{2,+2}$	0.039(18)	0.041(19)	0.0	0.064(19)	0.077(15)	0.039(16)	0.0	0.033(18)	0.033(18)	0.0
$P_{2,-2}$	0.019(18)	-0.054(19)	-0.041(19)	0.0	-0.048(15)	-0.024(15)	-0.058(18)	-0.028(19)	-0.048(19)	-0.035(18)
$P_{3,0}$	0.0	0.0	0.058(31)	0.0	-0.039(25)	0.0	0.0	0.0	0.0	0.0
$P_{3,+1}$	0.0	0.051(31)	0.0	0.0	0.045(24)	0.0	0.030(29)	0.0	0.0	0.0
$P_{3,-1}$	0.0	-0.042(31)	0.0	0.0	-0.036(23)	0.048(24)	-0.042(30)	0.047(30)	0.016(29)	0.052(29)
$P_{3,+2}$	0.0	0.0	0.0	0.0	0.032(24)	0.0	0.0	0.0	0.0	0.0
$P_{3,-2}$	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-0.030(30)	0.0	0.0
$P_{3,+3}$	0.271(27)	0.298(27)	0.315(28)	0.318(28)	0.270(22)	0.222(22)	0.280(27)	0.294(27)	0.313(27)	0.288(29)
$P_{3,-3}$	0.0	0.082(31)	0.0	-0.006(30)	-0.029(26)	0.0	0.0	0.0	-0.068(31)	0.0

Multipoles	C6	C6'	C7	C7'	C8	C8'	C9	C9'	C10	C10'
$P_{1,+1}$	0.0	-0.071(26)	-0.033(25)	-0.091(27)	0.0	0.052(27)	0.0	0.0	0.066(29)	-0.062(29)
$P_{1,-1}$	0.038(25)	0.0	-0.043(25)	0.047(25)	-0.030(26)	0.0	0.056(27)	0.0	0.0	0.091(28)
$P_{1,0}$	-0.030(24)	-0.043(26)	-0.083(25)	-0.037(24)	-0.033(27)	0.035(26)	0.0	-0.055(27)	0.0	0.0
$P_{2,0}$	0.0	0.055(19)	0.022(18)	0.0	0.047(17)	-0.028(16)	0.034(17)	0.0	-0.213(19)	-0.133(19)
$P_{2,+1}$	-0.063(18)	0.0	0.0	0.020(17)	-0.047(17)	-0.017(16)	0.023(16)	0.017(17)	-0.021(18)	0.0
$P_{2,-1}$	0.0	-0.036(19)	0.0	0.0	-0.063(17)	-0.029(16)	0.049(17)	0.053(17)	0.048(18)	-0.020(19)
$P_{2,+2}$	0.055(17)	0.018(16)	0.025(17)	0.025(17)	0.0	-0.017(16)	-0.067(16)	-0.020(15)	0.0	0.0
$P_{2,-2}$	0.018(17)	0.0	-0.058(16)	0.0	0.0	0.076(17)	0.023(16)	0.072(17)	0.0	-0.023(18)
$P_{3,0}$	-0.048(30)	0.0	0.0	-0.035(28)	0.036(30)	0.057(29)	0.035(29)	0.0	0.0	-0.053(31)
$P_{3,+1}$	0.0	-0.088(28)	-0.071(28)	0.0	-0.053(28)	0.088(28)	0.067(26)	0.0	0.0	0.052(30)
$P_{3,-1}$	0.0	-0.060(28)	0.0	0.078(26)	0.0	0.080(26)	0.0	0.0	0.0	0.0
$P_{3,+2}$	-0.029(28)	0.0	0.073(29)	0.0	0.050(28)	-0.069(28)	-0.161(27)	-0.036(28)	0.0	0.0
$P_{3,-2}$	0.313(27)	0.241(29)	0.209(27)	0.256(28)	0.341(27)	0.295(28)	0.272(26)	-0.288(28)	-0.049(30)	0.0
$P_{3,+3}$	-0.113(27)	-0.165(25)	-0.151(25)	-0.153(28)	0.0	0.074(26)	0.053(26)	0.0	0.334(28)	0.295(27)
$P_{3,-3}$	-0.053(27)	0.0	0.080(27)	0.0	0.0	-0.037(27)	0.0	-0.032(26)	0.0	0.0

Table 16. Multipole populations (e^-) of Carbon atoms of 17β-estradiol•½methanol.

Multipoles	C11	C11'	C12	C12'	C13	C13'	C14	C14'	C15	C15'
$P_{1,+1}$	-0.097(26)	0.0	-0.074(27)	0.0	-0.026(24)	0.0	0.0	0.0	0.0	-0.070(27)
$P_{1,-1}$	0.038(26)	0.0	0.0	0.049(25)	0.0	0.105(26)	0.032(25)	0.0	0.026(24)	0.076(26)
$P_{1,0}$	0.0	0.0	-0.039(23)	0.0	-0.027(26)	0.026(24)	-0.094(27)	0.0	0.034(24)	-0.053(25)
$P_{2,0}$	0.0	0.0	-0.044(18)	0.041(18)	0.026(18)	-0.031(17)	0.031(18)	0.020(17)	0.030(19)	-0.054(20)
$P_{2,+1}$	0.0	-0.045(18)	0.073(17)	0.067(17)	-0.052(17)	-0.095(17)	0.066(17)	-0.081(17)	0.0	-0.021(19)
$P_{2,-1}$	-0.095(17)	0.0	-0.034(17)	0.0	-0.024(17)	0.0	-0.023(17)	0.0	-0.071(18)	-0.059(19)
$P_{2,+2}$	0.0	0.047(17)	0.0	0.047(17)	0.0	0.0	0.0	0.0	0.070(18)	0.029(17)
$P_{2,-2}$	0.020(16)	-0.024(17)	-0.080(17)	-0.018(17)	0.0	0.058(17)	-0.025(16)	0.0	0.021(18)	-0.022(19)
$P_{3,0}$	-0.028(28)	0.036(30)	0.0	0.067(30)	0.044(30)	0.055(28)	-0.044(29)	0.064(26)	-0.039(30)	0.0
$P_{3,+1}$	-0.098(26)	-0.069(29)	-0.031(27)	-0.035(27)	-0.061(27)	0.085(27)	-0.094(28)	-0.042(28)	0.0	-0.048(29)
$P_{3,-1}$	0.0	-0.037(28)	0.044(27)	0.045(27)	0.0	0.099(26)	0.0	-0.113(27)	0.028(27)	0.0
$P_{3,+2}$	-0.042(28)	0.0	0.058(27)	0.0	0.096(28)	-0.036(28)	0.067(28)	0.0	-0.039(29)	0.0
$P_{3,-2}$	0.272(27)	0.295(28)	0.283(28)	0.267(27)	0.329(27)	0.332(27)	0.296(27)	0.307(27)	0.289(28)	0.236(30)
$P_{3,+3}$	-0.139(27)	-0.127(26)	-0.115(26)	-0.075(26)	-0.037(26)	0.034(26)	-0.099(25)	-0.077(28)	-0.115(28)	-0.181(28)
$P_{3,-3}$	0.0	0.049(27)	0.0	-0.033(26)	0.0	-0.077(28)	0.026(26)	0.060(27)	0.0	0.0

Multipoles	C16	C16'	C17	C17'	C18	C18'	C19
$P_{1,+1}$	0.0	-0.034(26)	0.028(20)	0.039(19)	-0.028(25)	-0.078(26)	-0.085(24)
$P_{1,-1}$	-0.031(25)	0.0	0.0	0.0	0.034(24)	0.097(24)	-0.028(26)
$P_{1,0}$	-0.061(26)	-0.049(24)	-0.067(18)	0.0	-0.034(24)	0.046(24)	0.025(25)
$P_{2,0}$	0.033(20)	0.0	-0.018(13)	0.028(14)	-0.017(17)	0.020(17)	0.080(21)
$P_{2,+1}$	0.0	-0.025(19)	0.052(13)	0.014(13)	-0.039(17)	0.0	0.0
$P_{2,-1}$	0.0	-0.050(20)	0.0	0.0	-0.016(16)	0.055(17)	0.020(19)
$P_{2,+2}$	0.0	0.0	0.0	0.0	0.054(18)	0.0	0.020(19)
$P_{2,-2}$	-0.019(18)	-0.030(18)	-0.078(13)	-0.031(13)	0.023(17)	0.059(18)	0.0
$P_{3,0}$	0.041(30)	0.059(30)	-0.074(22)	-0.066(21)	-0.028(29)	0.054(27)	0.177(32)
$P_{3,+1}$	-0.091(29)	0.0	-0.080(21)	-0.087(21)	0.0	0.110(28)	0.109(30)
$P_{3,-1}$	0.034(28)	0.022(29)	0.0	0.0	0.0	0.0	0.0
$P_{3,+2}$	0.0	-0.070(29)	0.074(22)	0.0	0.039(27)	0.072(28)	0.0
$P_{3,-2}$	0.274(28)	0.205(28)	0.212(21)	0.224(21)	0.212(26)	-0.229(28)	0.299(31)
$P_{3,+3}$	-0.135(25)	-0.116(28)	-0.076(21)	0.0	0.0	0.078(27)	0.091(30)
$P_{3,-3}$	0.061(26)	-0.039(27)	0.0	-0.021(20)	0.0	0.044(26)	0.0

Table 17. Multipole populations (e^-) of Carbon atoms of 17β-estradiol•½methanol continued.

Atoms	$P_{1,0}$	$P_{2,0}$
H1O	0.121(19)	0.005(28)
H2O	0.125(21)	0.002(28)
H1	0.109(24)	-0.007(31)
H2	0.107(22)	0.066(32)
H4	0.127(23)	-0.018(30)
H6A	0.105(15)	-0.010(19)
H6B	0.105(15)	-0.010(19)
H7A	0.134(15)	0.034(20)
H7B	0.134(15)	0.034(20)
H8	0.150(23)	-0.029(31)
H9	0.089(22)	0.028(29)
H11A	0.110(16)	-0.015(21)
H11B	0.110(16)	-0.015(21)
H12A	0.099(16)	0.019(20)
H12B	0.099(16)	0.019(20)
H14	0.118(24)	-0.006(29)
H15A	0.070(17)	0.018(22)
H15B	0.070(17)	0.018(22)
H16A	0.132(16)	-0.005(22)
H16B	0.132(16)	-0.005(22)
H17	0.167(24)	0.041(33)
H18A	0.106(13)	-0.035(17)
H18B	0.106(13)	-0.035(17)
H18C	0.106(13)	-0.035(17)

Atoms	$P_{1,0}$	$P_{2,0}$
H1O'	0.127(19)	0.018(27)
H2O'	0.129(20)	0.012(28)
H1'	0.191(23)	0.006(29)
H2'	0.150(23)	0.043(34)
H4'	0.112(22)	0.049(28)
H6C	0.138(16)	0.024(22)
H6D	0.138(16)	0.024(22)
H7C	0.137(15)	0.051(21)
H7D	0.137(15)	0.051(21)
H8'	0.148(22)	0.056(30)
H9'	0.127(24)	0.065(32)
H11C	0.139(16)	0.033(22)
H11D	0.139(16)	0.033(22)
H12C	0.140(16)	-0.026(20)
H12D	0.140(16)	-0.026(20)
H14'	0.176(24)	0.058(31)
H15C	0.075(17)	0.062(23)
H15D	0.075(17)	0.062(23)
H16C	0.094(17)	-0.033(22)
H16D	0.094(17)	-0.033(22)
H17'	0.219(23)	0.062(35)
H18D	0.102(13)	0.012(17)
H18E	0.102(13)	0.012(17)
H18F	0.102(13)	0.012(17)
H3O	0.088(19)	-0.043(30)
H19A	0.183(13)	-0.036(19)
H19B	0.183(13)	-0.036(19)
H19C	0.183(13)	-0.036(19)

Table 18. Multipole populations (e^-) of Hydrogen atoms of 17β-estradiol•½methanol.

Bond	$\rho(r_c)$	$\nabla^2\rho(r_c)$	R_{ij}	d_1	d_2	λ_1	λ_2	λ_3	ε
O1 – C3	1.992	-18.666	1.3731	0.8342	0.5389	-17.30	-13.85	12.49	0.25
O1' – C3'	2.101	-18.114	1.3692	0.8106	0.5586	-17.16	-15.42	14.46	0.11
O1 – H1O	2.379	-31.187	0.9702	0.7400	0.2302	-37.16	-36.51	42.48	0.02
O1' – H1O'	2.308	-28.991	0.9701	0.7502	0.2199	-37.32	-35.43	43.76	0.05
O2 – C17	1.734	-8.541	1.4259	0.8182	0.6078	-13.32	-11.42	16.21	0.17
O2' – C17'	1.863	-10.326	1.4294	0.8159	0.6136	-14.80	-13.62	18.10	0.09
O2 – H2O	2.303	-30.051	0.9704	0.7491	0.2213	-37.23	-35.63	42.80	0.05
O2' – H2O'	2.311	-26.715	0.9701	0.7415	0.2286	-35.18	-34.78	43.25	0.01
C1 – C2	2.160	-20.204	1.3930	0.7046	0.6884	-16.25	-12.87	8.92	0.26
C1' – C2'	2.111	-19.897	1.3934	0.7349	0.6585	-15.99	-12.24	8.32	0.31
C1 – C10	2.088	-18.453	1.4011	0.6823	0.7187	-15.30	-12.20	9.06	0.25
C1' – C10'	2.097	-19.229	1.4036	0.7295	0.6742	-15.82	-12.35	8.94	0.28
C1 – H1	1.807	-15.039	1.0804	0.6524	0.4280	-16.66	-14.94	16.55	0.12
C1' – H1'	1.785	-16.604	1.0800	0.6082	0.4718	-15.80	-13.51	12.70	0.17
C2 – C3	2.172	-21.192	1.3969	0.6614	0.7355	-16.77	-13.88	9.45	0.21
C2' – C3'	2.103	-18.329	1.3946	0.7454	0.6492	-16.33	-11.74	9.74	0.39
C2 – H2	1.884	-17.271	1.0801	0.6619	0.4182	-17.49	-16.52	16.74	0.06
C2' – H2'	1.891	-18.440	1.0800	0.6345	0.4456	-17.47	-15.48	14.50	0.13
C3 – C4	2.228	-21.634	1.3931	0.7152	0.6779	-17.78	-13.87	10.02	0.28
C3' – C4'	2.156	-19.354	1.3948	0.7118	0.6830	-16.37	-13.24	10.26	0.24
C4 – C5	2.095	-18.890	1.3993	0.6556	0.7437	-15.71	-11.94	8.76	0.32
C4' – C5'	2.078	-18.328	1.4012	0.6942	0.7070	-15.69	-11.90	9.27	0.32
C4 – H4	1.779	-12.634	1.0803	0.6507	0.4295	-15.43	-14.16	16.96	0.09
C4' – H4'	1.932	-18.229	1.0801	0.6569	0.4232	-17.81	-16.99	16.56	0.05
C5 – C6	1.705	-12.450	1.5112	0.7592	0.7520	-11.83	-10.57	9.95	0.12
C5' – C6'	1.694	-11.252	1.5127	0.7635	0.7492	-11.64	-9.88	10.26	0.18

Table 19. Topological properties of bond critical points in 17β-estradiol•½methanol.

Bond	$\rho(r_c)$	$\nabla^2\rho(r_c)$	R_{ij}	d_1	D_2	λ_1	λ_2	λ_3	ε
C5 – C10	2.155	-20.813	1.4072	0.7180	0.6892	-16.33	-13.65	9.17	0.20
C5' – C10'	2.073	-18.203	1.4084	0.6742	0.7342	-15.25	-12.23	9.28	0.25
C6 – C7	1.583	-10.047	1.5249	0.7796	0.7453	-10.69	-9.50	10.14	0.13
C6' – C7'	1.626	-10.314	1.5248	0.7435	0.7813	-10.90	-9.62	10.20	0.13
C6 – H6A	1.691	-10.161	1.0900	0.6479	0.4421	-14.54	-12.47	16.85	0.17
C6 – H6B	1.776	-12.170	1.0923	0.6623	0.4300	-15.70	-14.71	18.24	0.07
C6' – H6C	1.881	-14.581	1.0906	0.6503	0.4403	-16.63	-14.99	17.04	0.11
C6' – H6D	1.872	-14.981	1.0901	0.6465	0.4436	-16.68	-14.86	16.57	0.12
C7 – C8	1.590	-9.180	1.5269	0.7957	0.7312	-10.18	-9.20	10.20	0.11
C7' – C8'	1.625	-9.958	1.5289	0.7494	0.7796	-10.77	-9.54	10.35	0.13
C7 – H7A	1.948	-16.835	1.0900	0.6574	0.4326	-18.12	-16.09	17.38	0.13
C7 – H7B	1.807	-14.807	1.0905	0.6387	0.4518	-15.99	-14.29	15.47	0.12
C7' – H7C	1.964	-17.201	1.0903	0.6551	0.4351	-18.26	-16.04	17.09	0.14
C7' – H7D	1.807	-14.724	1.0912	0.6361	0.4550	-15.79	-14.28	15.35	0.11
C8 – C9	1.581	-9.450	1.5438	0.7668	0.7770	-10.22	-9.47	10.24	0.08
C8' – C9'	1.545	-7.983	1.5457	0.7759	0.7697	-9.94	-8.59	10.54	0.16
C8 – C14	1.682	-11.473	1.5223	0.7540	0.7683	-11.40	-10.29	10.22	0.11
C8' – C14'	1.625	-10.656	1.5235	0.7202	0.8033	-11.05	-9.55	9.94	0.16
C8 – H8	1.813	-12.664	1.1003	0.6650	0.4353	-15.49	-15.16	17.98	0.02
C8' – H8'	1.923	-17.748	1.1009	0.6606	0.4404	-17.42	-16.56	16.23	0.05
C9 – C10	1.688	-11.912	1.5246	0.7404	0.7842	-11.75	-10.36	10.19	0.13
C9' – C10'	1.584	-9.752	1.5281	0.7594	0.7686	-10.43	-9.44	10.12	0.10
C9 – C11	1.489	-8.316	1.5378	0.7931	0.7447	-9.77	-8.35	9.80	0.17
C9' – C11'	1.585	-9.071	1.5412	0.7351	0.8060	-10.51	-9.12	10.56	0.15
C9 – H9	1.879	-15.456	1.1000	0.6783	0.4217	-17.66	-16.23	18.44	0.09
C9' – H9'	1.956	-17.951	1.1001	0.6668	0.4333	-18.16	-16.92	17.12	0.07

Table 20. Topological properties of bond critical points in 17β-estradiol•½methanol continued.

Bond	$\rho(r_c)$	$\nabla^2\rho(r_c)$	R_{ij}	d_1	D_2	λ_1	λ_2	λ_3	ε
C11 – C12	1.589	-10.204	1.5382	0.7492	0.7890	-10.57	-9.72	10.09	0.09
C11' – C12'	1.541	-9.336	1.5408	0.7628	0.7779	-9.91	-9.41	9.98	0.05
C11 – H11A	1.789	-11.786	1.0901	0.6602	0.4299	-15.68	-14.41	18.30	0.09
C11 – H11B	1.813	-12.082	1.0900	0.6636	0.4264	-15.98	-14.81	18.71	0.08
C11' – H11C	1.810	-14.683	1.0924	0.6453	0.4472	-15.97	-14.68	15.96	0.09
C11' – H11D	1.845	-14.612	1.0902	0.6489	0.4413	-16.32	-14.86	16.57	0.10
C12 – C13	1.658	-11.077	1.5275	0.7506	0.7769	-11.03	-10.22	10.17	0.08
C12' – C13'	1.635	-9.576	1.5307	0.7501	0.7806	-11.01	-9.45	10.89	0.16
C12 – H12A	1.960	-16.160	1.0903	0.6768	0.4135	-18.65	-17.02	19.50	0.10
C12 – H12B	1.698	-12.630	1.0914	0.6421	0.4493	-14.77	-13.44	15.58	0.10
C12' – H12C	1.897	-14.894	1.0903	0.6570	0.4333	-17.33	-15.47	17.90	0.12
C12' – H12D	1.693	-10.342	1.0908	0.6354	0.4554	-14.31	-12.11	16.08	0.18
C13 – C14	1.538	-8.278	1.5423	0.7589	0.7834	-9.58	-8.85	10.15	0.08
C13' – C14'	1.643	-9.762	1.5434	0.7891	0.7543	-10.34	-9.90	10.48	0.04
C13 – C17	1.624	-8.277	1.5379	0.7470	0.7909	-10.54	-9.99	12.26	0.06
C13' – C17'	1.510	-6.686	1.5423	0.7449	0.7974	-9.53	-8.74	11.58	0.09
C13 – C18	1.668	-9.648	1.5368	0.7767	0.7602	-10.68	-10.13	11.16	0.05
C13' – C18'	1.715	-10.914	1.5332	0.7625	0.7707	-11.10	-10.93	11.11	0.01
C14 – C15	1.580	-9.879	1.5414	0.7578	0.7836	-10.46	-9.46	10.04	0.11
C14' – C15'	1.586	-9.229	1.5363	0.7506	0.7858	-10.41	-9.10	10.28	0.14
C14 – H14	1.910	-15.081	1.1001	0.6761	0.4240	-17.45	-16.21	18.58	0.08
C14' – H14'	2.006	-20.475	1.1000	0.6528	0.4472	-18.50	-17.49	15.51	0.06
C15 – C16	1.525	-8.303	1.5532	0.7550	0.7982	-10.05	-8.63	10.38	0.17
C15' – C16'	1.492	-7.757	1.5508	0.8012	0.7496	-9.89	-8.13	10.26	0.22
C15 – H15A	1.763	-11.798	1.0901	0.6645	0.4256	-16.19	-14.26	18.65	0.14
C15 – H15B	1.777	-10.781	1.0909	0.6711	0.4198	-15.74	-14.73	19.69	0.07

Table 21. Topological properties of bond critical points in 17β-estradiol•½methanol continued.

Bond	$\rho(r_c)$	$\nabla^2\rho(r_c)$	R_{ij}	d_1	D_2	λ_1	λ_2	λ_3	ε
C15' – H15C	1.882	-15.052	1.0903	0.6688	0.4216	-18.03	-15.33	18.32	0.18
C15' – H15D	1.751	-13.044	1.0913	0.6552	0.4361	-15.90	-14.21	17.07	0.12
C16 – C17	1.638	-9.824	1.5461	0.7828	0.7633	-11.30	-10.29	11.77	0.10
C16' – C17'	1.542	-7.493	1.5512	0.7795	0.7717	-9.98	-9.31	11.80	0.07
C16 – H16A	1.906	-15.286	1.0901	0.6486	0.4414	-16.96	-15.61	17.28	0.09
C16 – H16B	1.797	-13.408	1.0905	0.6364	0.4541	-14.93	-14.58	16.11	0.02
C16' – H16C	1.703	-8.472	1.0901	0.6520	0.4381	-14.36	-12.68	18.56	0.13
C16' – H16D	1.678	-8.319	1.0901	0.6487	0.4414	-13.95	-12.55	18.18	0.11
C17 – H17	2.018	-17.771	1.1000	0.6630	0.4371	-19.36	-18.82	20.41	0.03
C17' – H17'	2.067	-20.809	1.1006	0.6409	0.4597	-20.06	-18.79	18.05	0.07
C18 – H18A	1.812	-11.307	1.0600	0.6184	0.4416	-14.71	-13.64	17.05	0.08
C18 – H18B	1.844	-14.261	1.0605	0.6164	0.4441	-15.77	-14.74	16.25	0.07
C18 – H18C	1.850	-13.230	1.0603	0.6200	0.4403	-15.57	-14.56	16.90	0.07
C18' – H18D	1.762	-12.273	1.0691	0.6267	0.4424	-15.13	-14.29	17.15	0.06
C18' – H18E	1.910	-16.290	1.0611	0.6251	0.4360	-17.09	-15.73	16.53	0.09
C18' – H18F	1.933	-14.147	1.0610	0.6344	0.4265	-17.57	-14.76	18.18	0.19
O3 – C19	1.964	-12.936	1.4239	0.8367	0.5872	-14.50	-13.07	14.64	0.11
O3 – H3O	2.346	-19.388	0.9417	0.7160	0.2257	-35.13	-33.93	49.67	0.04
C19 – H19A	1.785	-12.350	1.0820	0.6237	0.4583	-15.47	-13.65	16.77	0.13
C19 – H19B	1.970	-19.275	1.0731	0.6177	0.4554	-18.20	-15.96	14.88	0.14
C19 – H19C	1.911	-14.353	1.0702	0.6159	0.4543	-17.14	-12.99	15.78	0.32

Table 22. Topological properties of bond critical points in 17β-estradiol•½methanol continued.

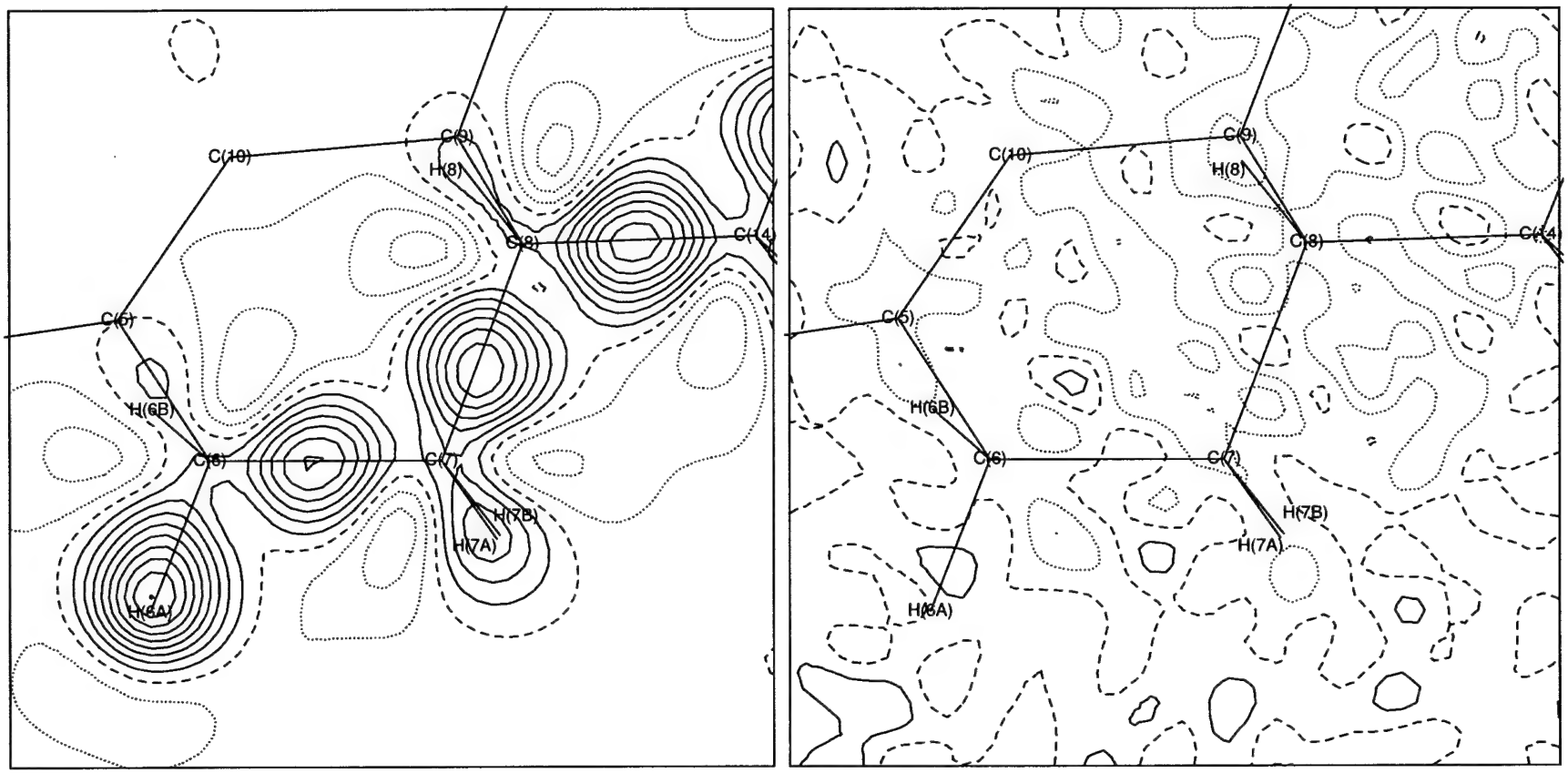

Figure 3. Dynamic model map and residual map in the C6 – C7 – C8 plane of 17β-estradiol•½methanol. Contour intervals are 0.05 eÅ^{-3} with solid lines positive, dashed lines zero, and dotted lines negative.

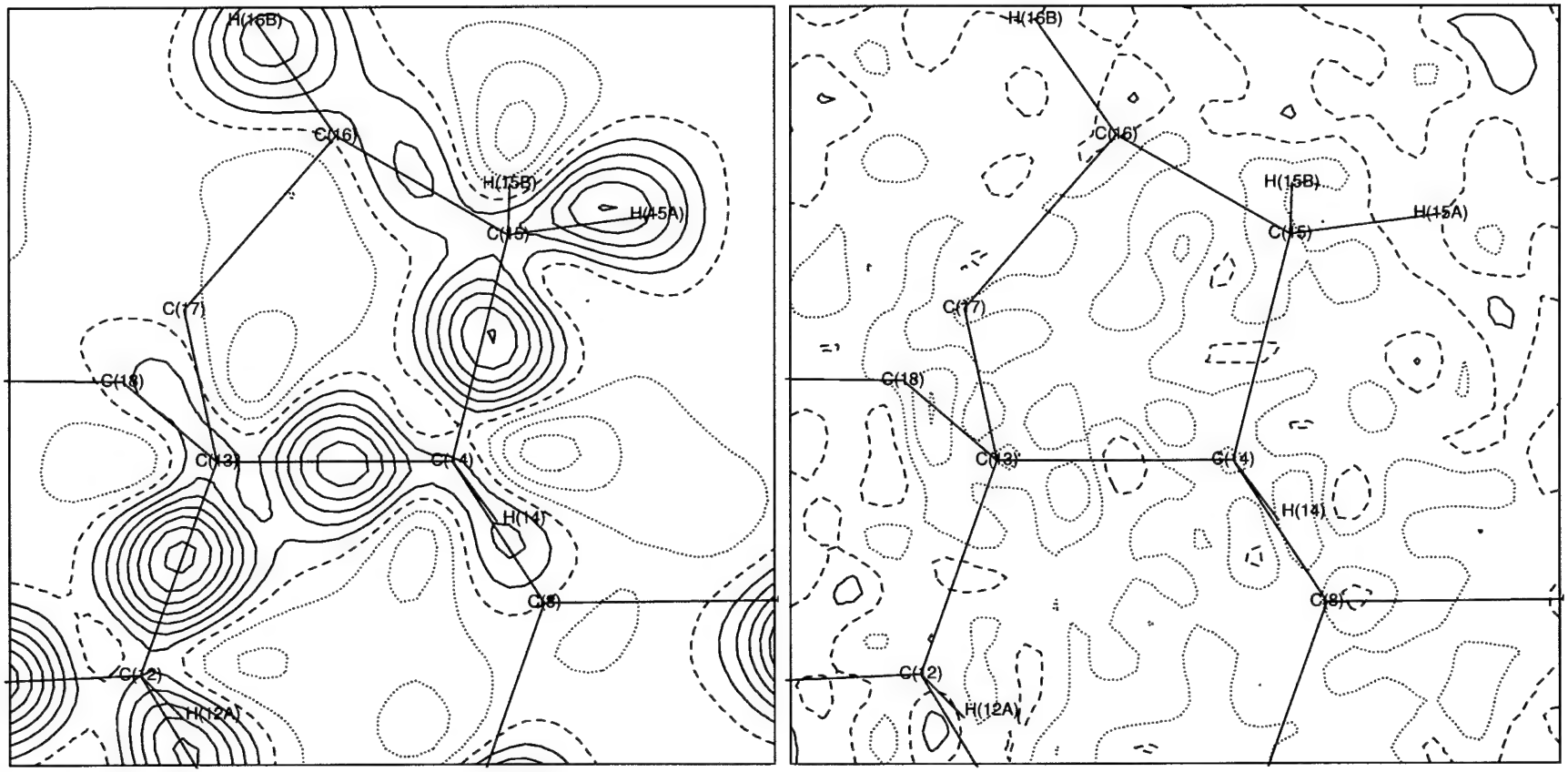

Figure 4. Dynamic model map and residual map in the C13 – C14 – C15 plane of 17β-estradiol•½methanol. Contour intervals are 0.05 eÅ^{-3} with solid lines positive, dashed lines zero, and dotted lines negative.

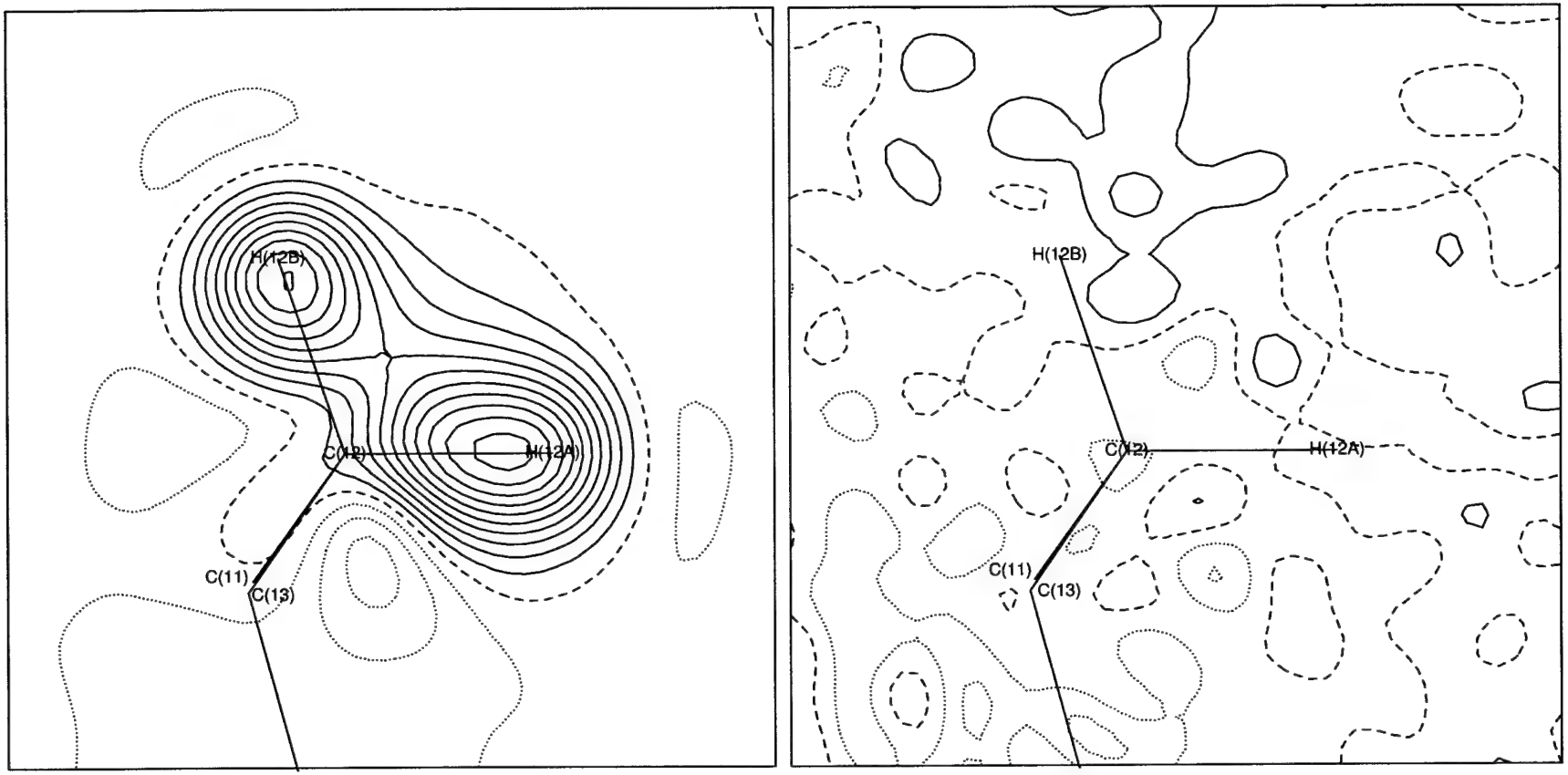

Figure 5. Dynamic model map and residual map in the C12 – H12A – H12B plane of 17β-estradiol•½methanol. Contour intervals are 0.05 e$\AA^{-3}$ with solid lines positive, dashed lines zero, and dotted lines negative.

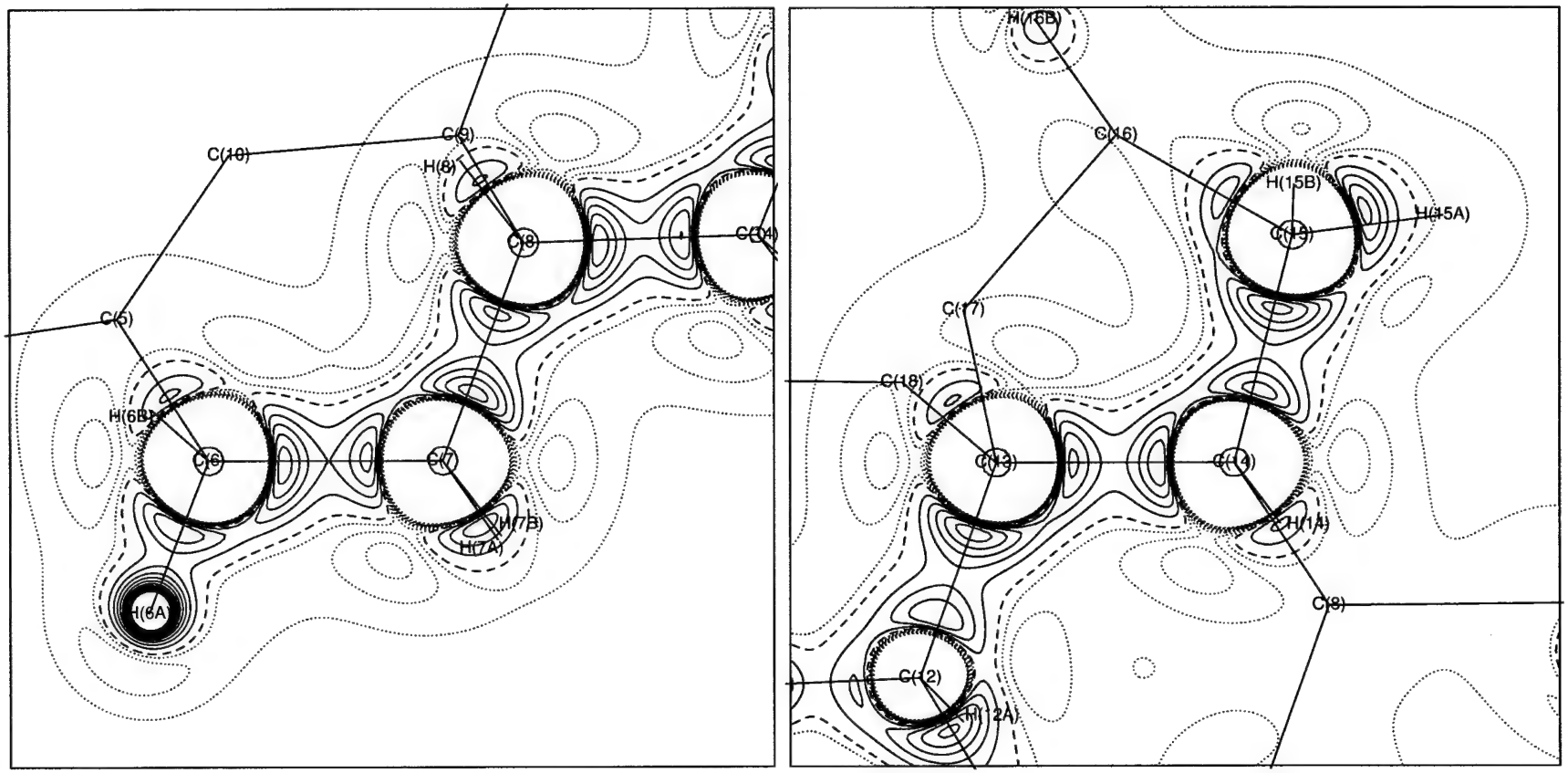

Figure 6. The Laplacian of the total electron density of atoms at rest in the C6 – C7 – C8 and C13 – C14 – C15 planes of 17β-estradiol•½methanol. Contour intervals are 5 eÅ^{-5} starting at 5 eÅ^{-5} (solid blue lines), -2 eÅ^{-5} starting at -2 eÅ^{-5} (dotted red lines), and the dashed line equals 0 eÅ^{-5}.

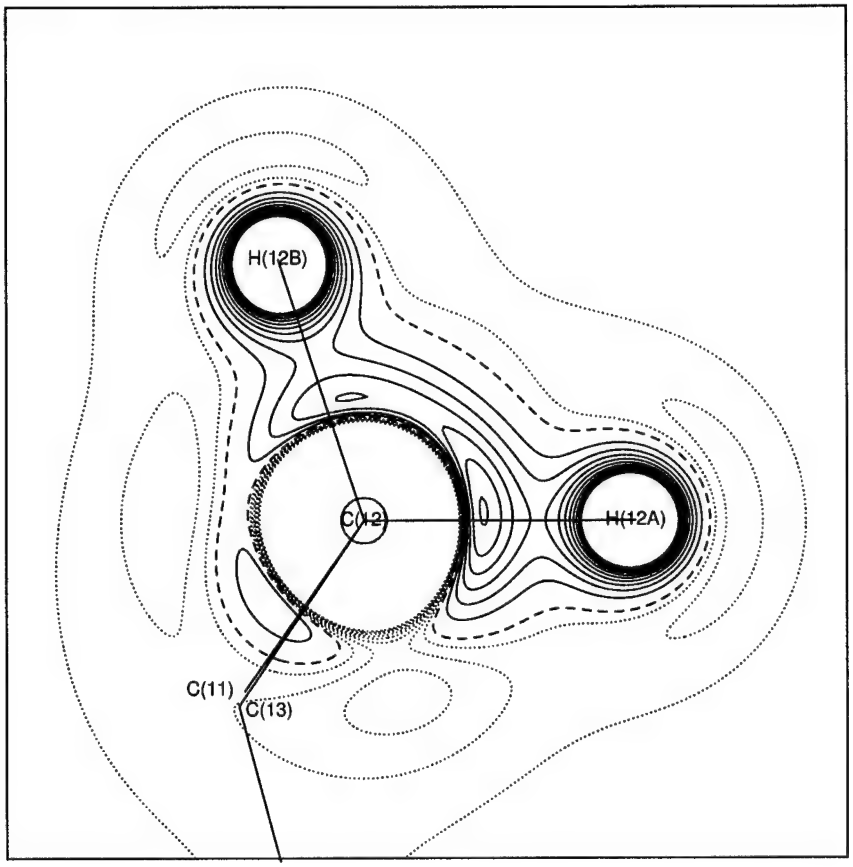

Figure 7. The Laplacian of the total electron density of atoms at rest in the H12A – C12 – H12B plane of 17β-estradiol•½methanol. Contour intervals are 5 eÅ^{-5} starting at 5 eÅ^{-5} (solid blue lines), -2 eÅ^{-5} starting at -2 eÅ^{-5} (dotted red lines), and the dashed line plots 0 eÅ^{-5}.

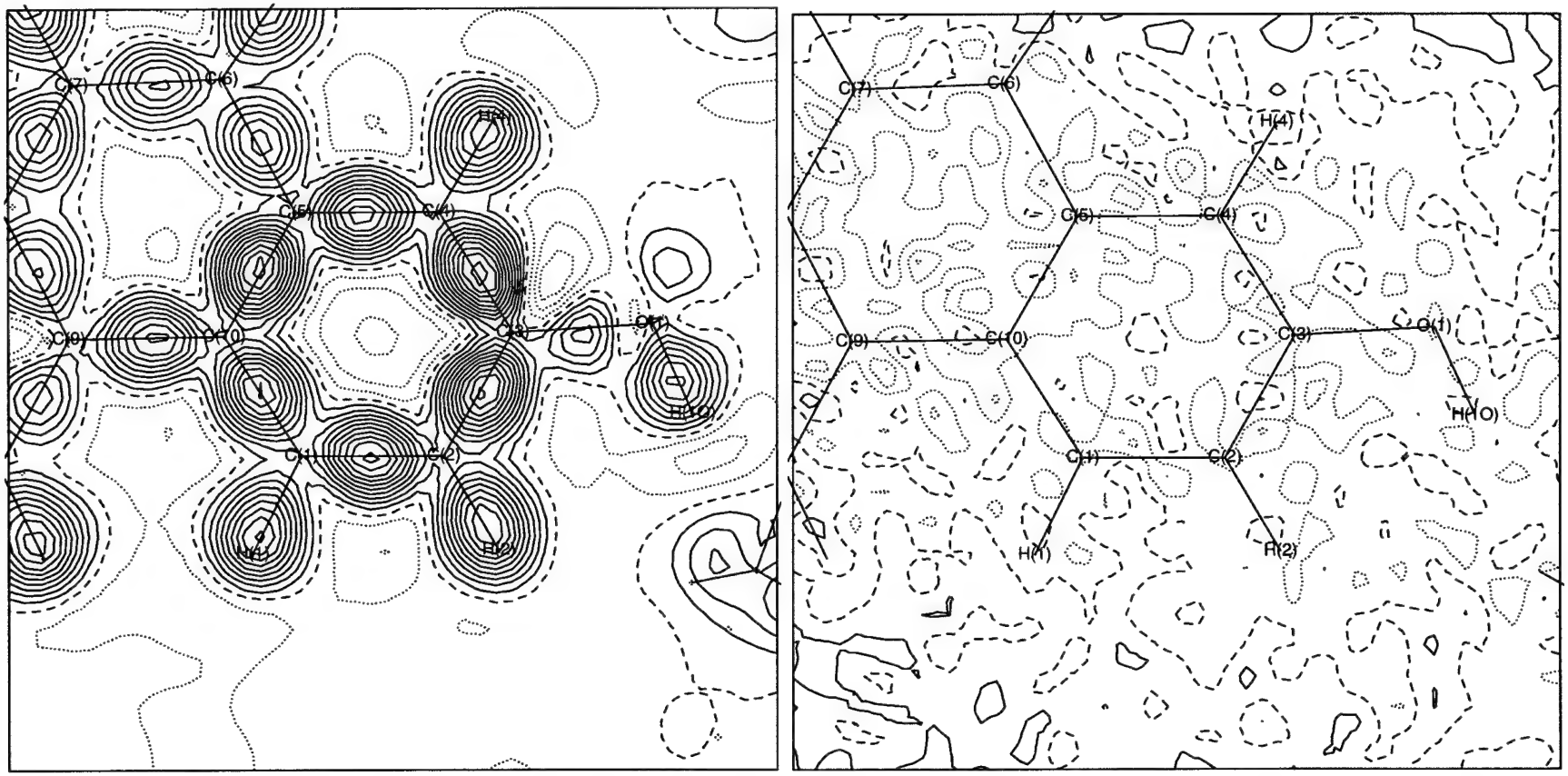

Figure 8. Dynamic model map and residual map in the plane of the aromatic ring of molecule 1 of 17β-estradiol•½methanol. Contour intervals are 0.05 eÅ^{-3} with solid lines positive, dashed lines zero, and dotted lines negative.

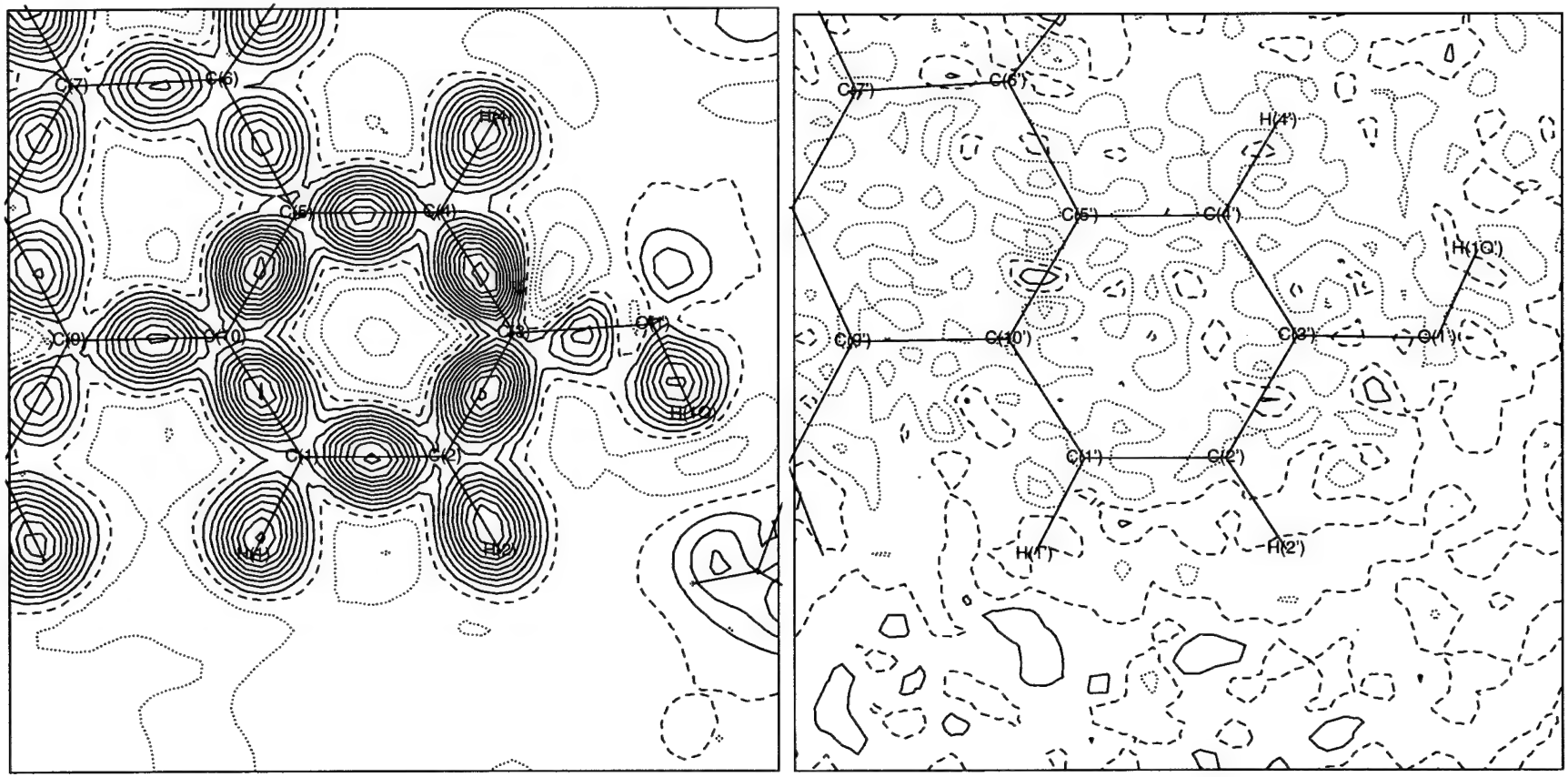

Figure 9. Dynamic model map and residual map in the plane of the aromatic ring of molecule 2 of 17β-estradiol•½methanol. Contour intervals are 0.05 eÅ^{-3} with solid lines positive, dashed lines zero, and dotted lines negative.

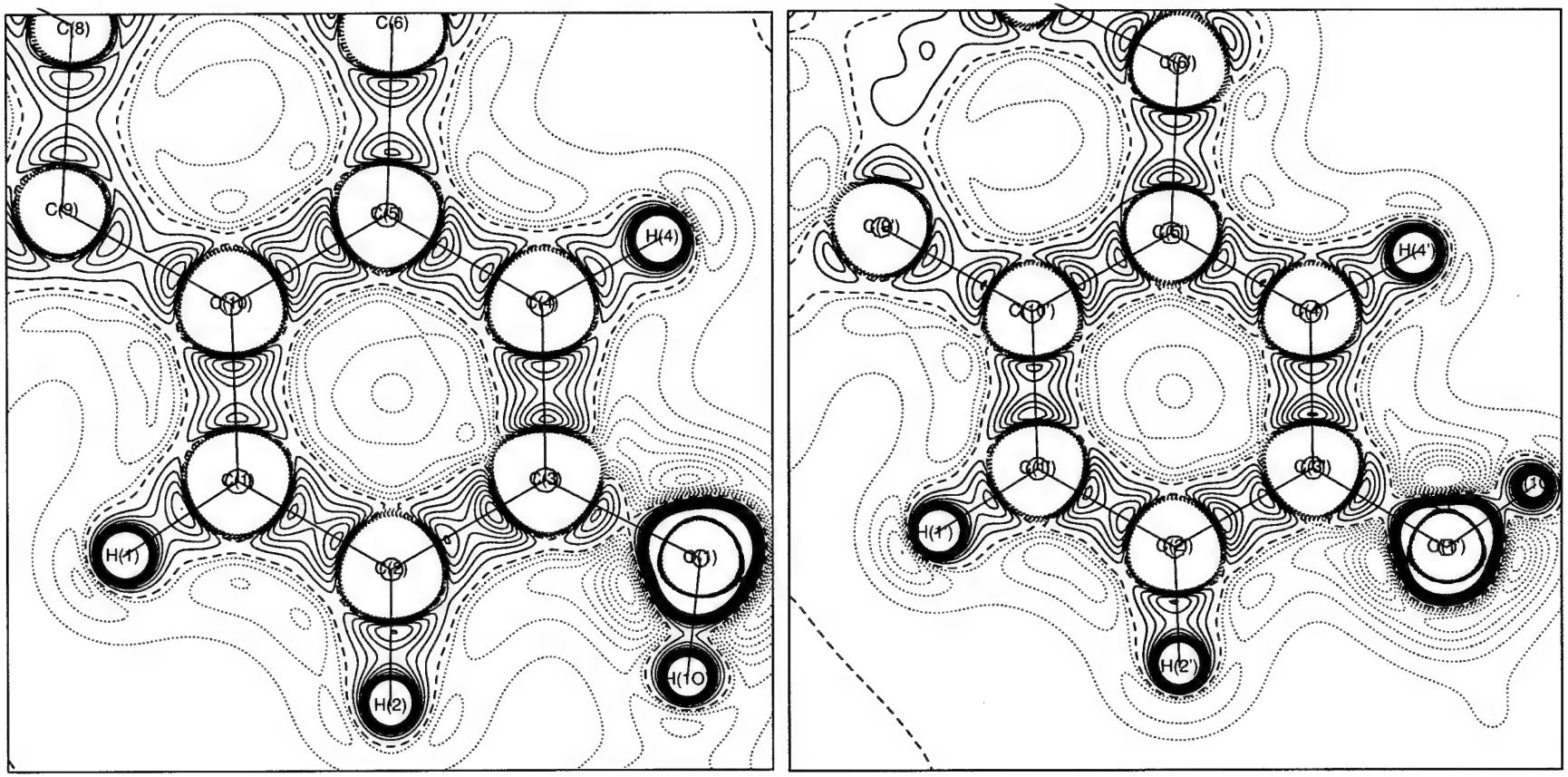

Figure 10. The Laplacian of the total electron density of atoms at rest in the plane of the aromatic rings of 17β-estradiol•½methanol. Contour intervals are 5 eÅ^{-5} starting at 5 eÅ^{-5} (solid blue lines), -2 eÅ^{-5} starting at -2 eÅ^{-5} (dotted red lines), and the dashed line plots 0 eÅ^{-5}.

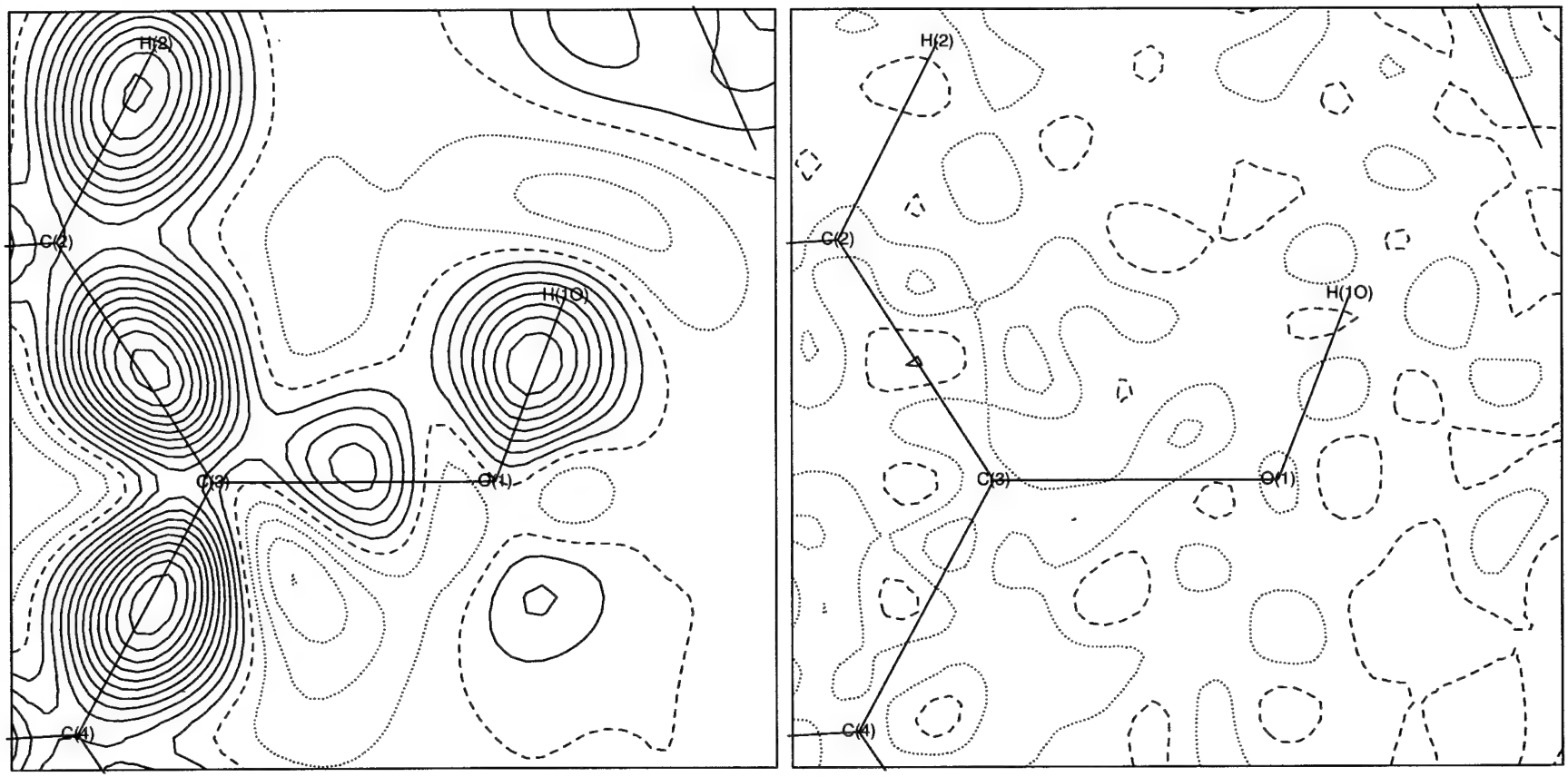

Figure 11. Dynamic model map and residual map in the C3 – O1 – H1O plane of 17β-estradiol•½methanol. Contour intervals are 0.05 eÅ^{-3} with solid lines positive, dashed lines zero, and dotted lines negative.

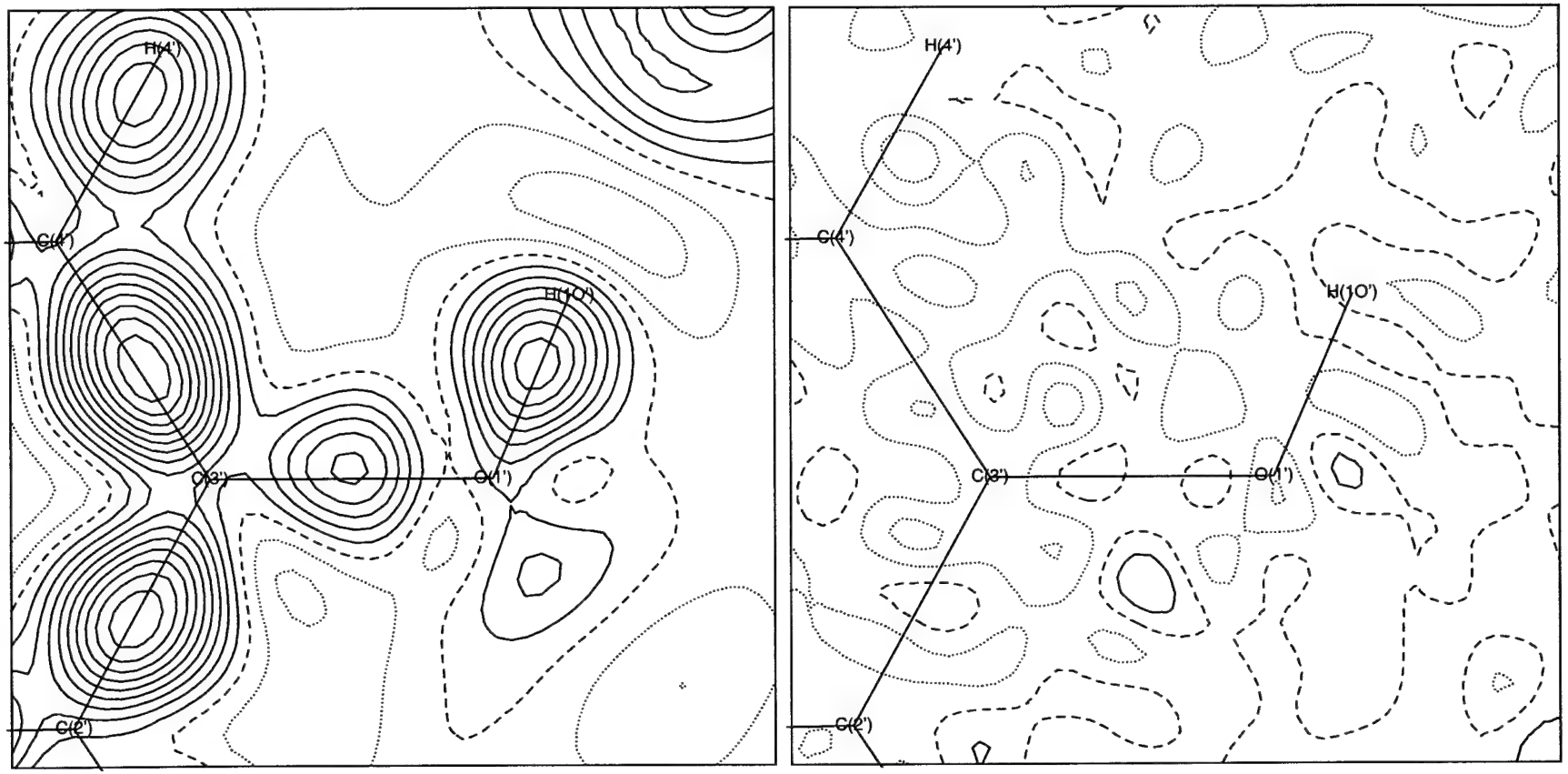

Figure 12. Dynamic model map and residual map in the C3' – O1' – H1O' plane of 17β-estradiol•½methanol. Contour intervals are 0.05 eÅ^{-3} with solid lines positive, dashed lines zero, and dotted lines negative.

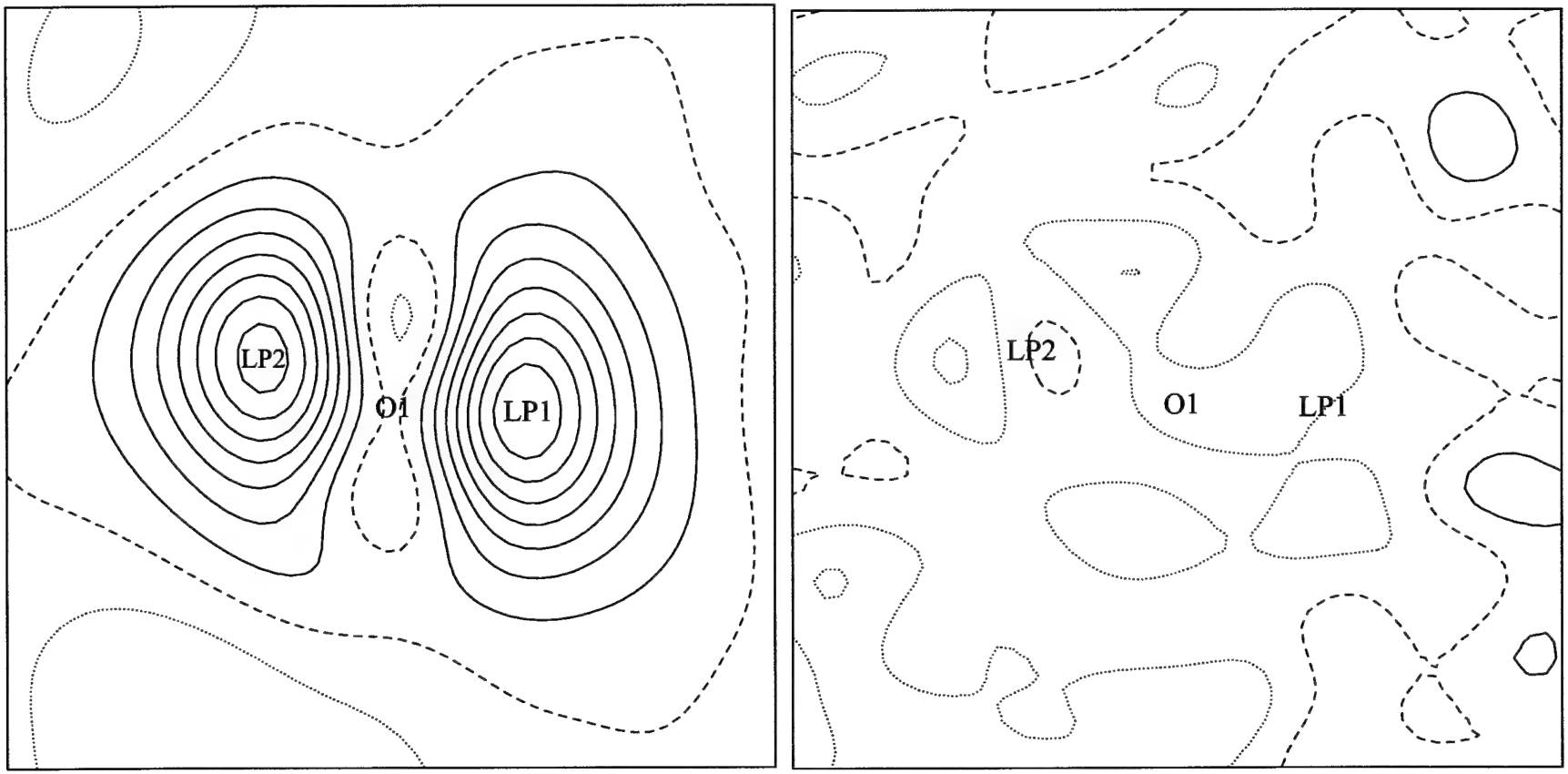

Figure 13. Dynamic model map and residual map in the plane of the lone pairs of O1 of 17β-estradiol•½methanol. Contour intervals are 0.05 e$\AA^{-3}$ with solid lines positive, dashed lines zero, and dotted lines negative.

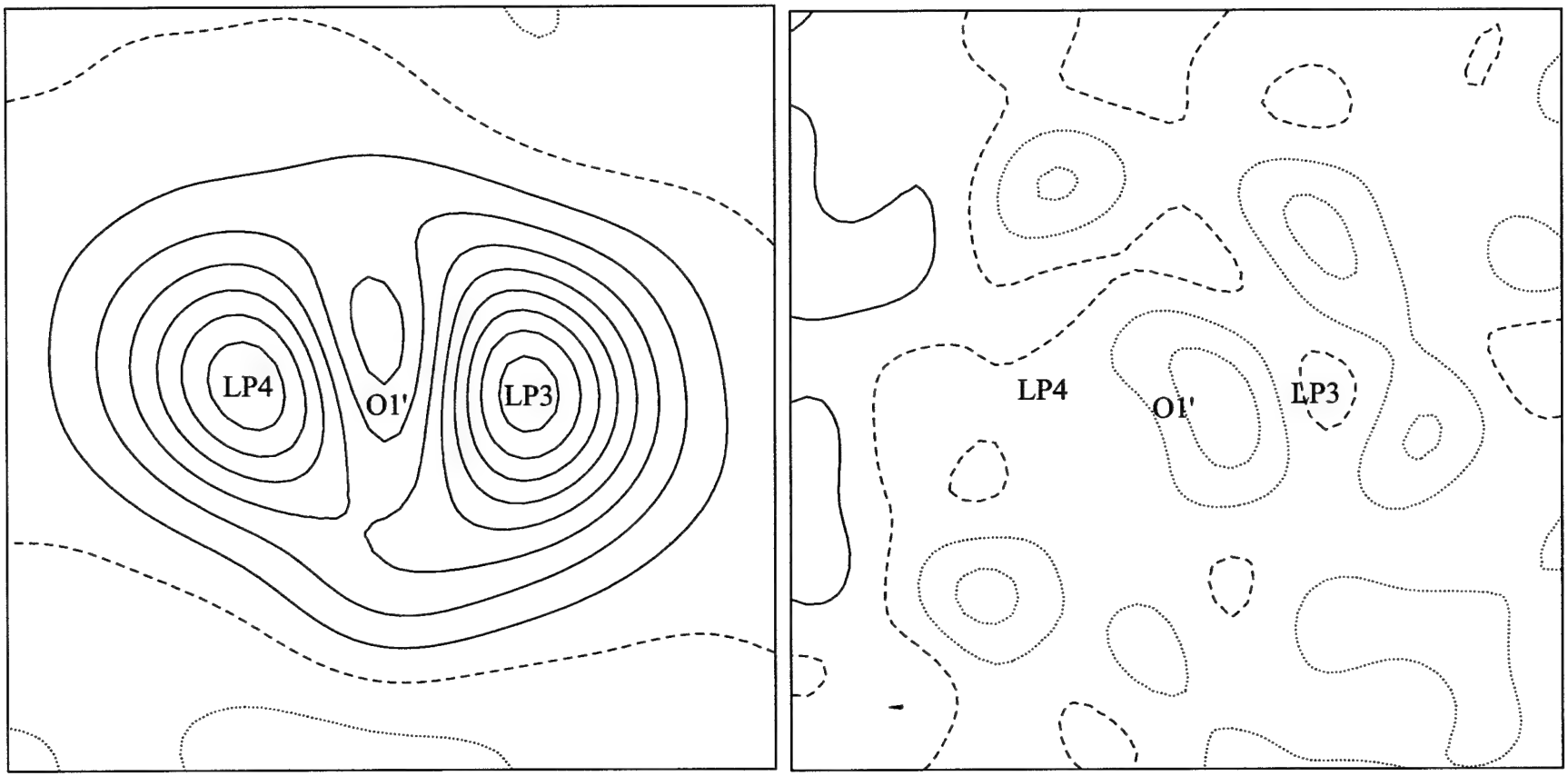

Figure 14. Dynamic model map and residual map in the plane of the lone pairs of O1' of 17β-estradiol•½methanol. Contour intervals are 0.05 eÅ^{-3} with solid lines positive, dashed lines zero, and dotted lines negative.

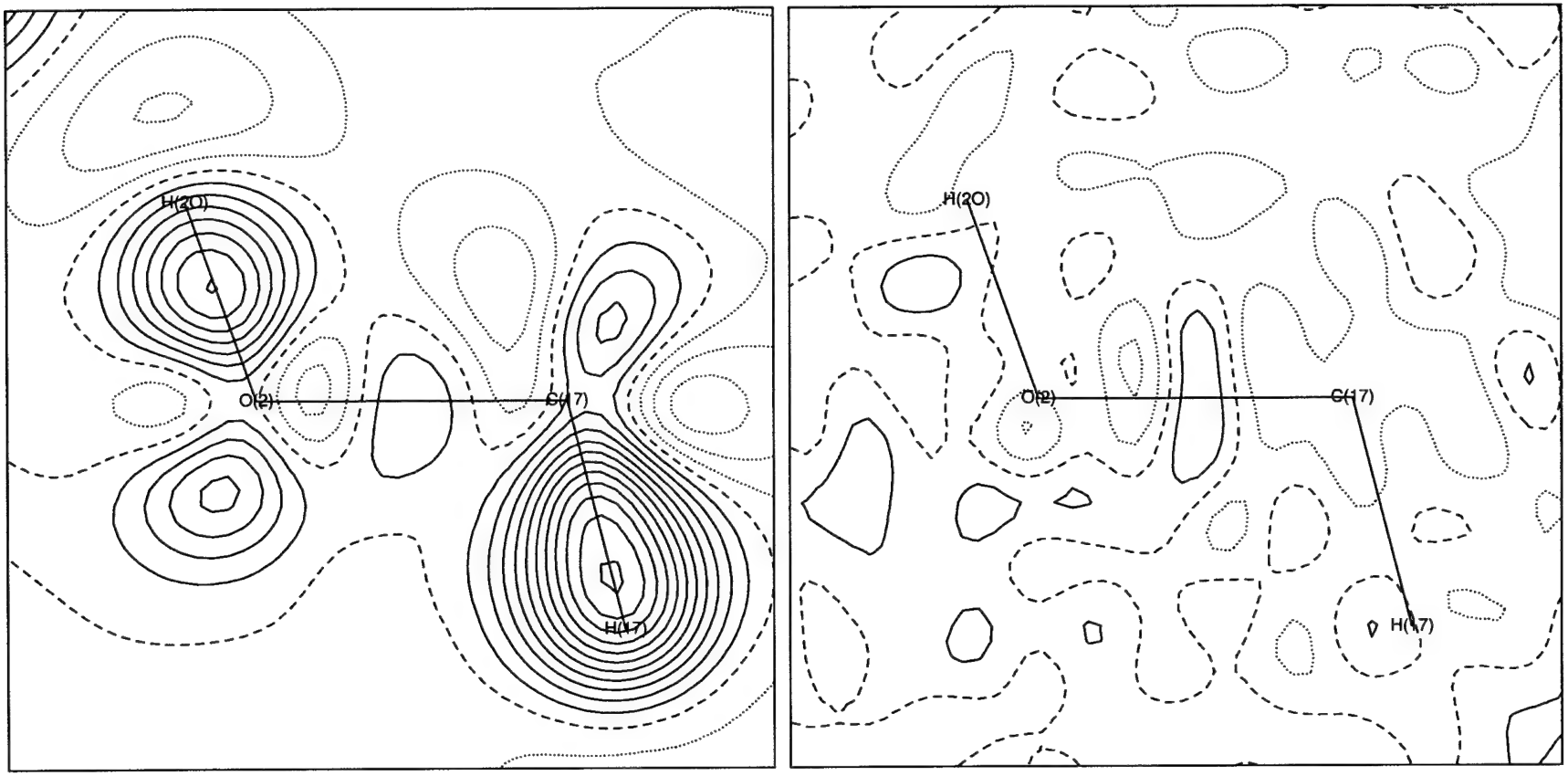

Figure 15. Dynamic model map and residual map in the C17 – O2 – H2O plane of 17β-estradiol•½methanol. Contour intervals are 0.05 eÅ^{-3} with solid lines positive, dashed lines zero, and dotted lines negative.

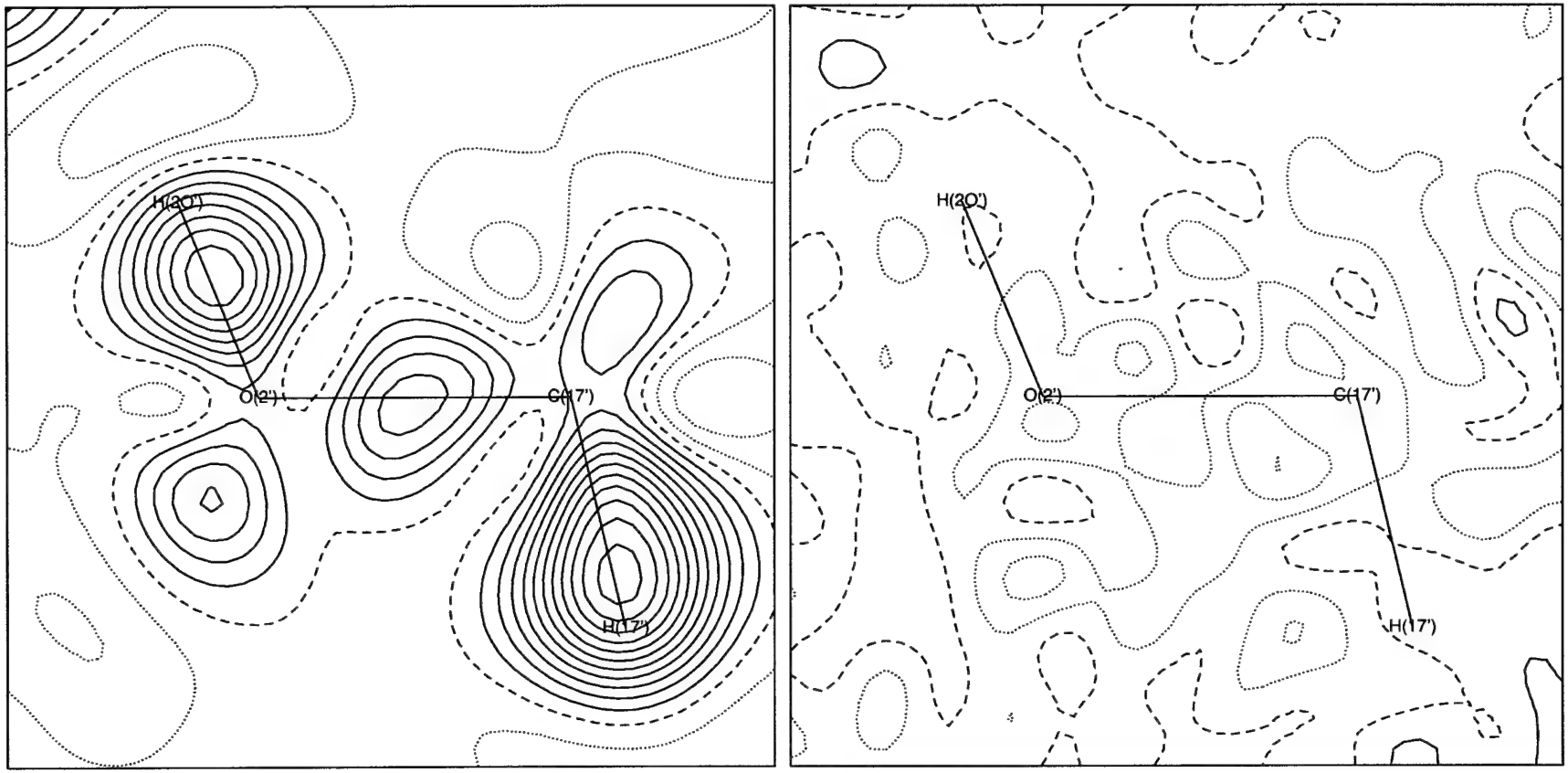

Figure 16. Dynamic model map and residual map in the C17' – O2' – H2O' plane of 17β-estradiol•½methanol. Contour intervals are 0.05 eÅ^{-3} with solid lines positive, dashed lines zero, and dotted lines negative.

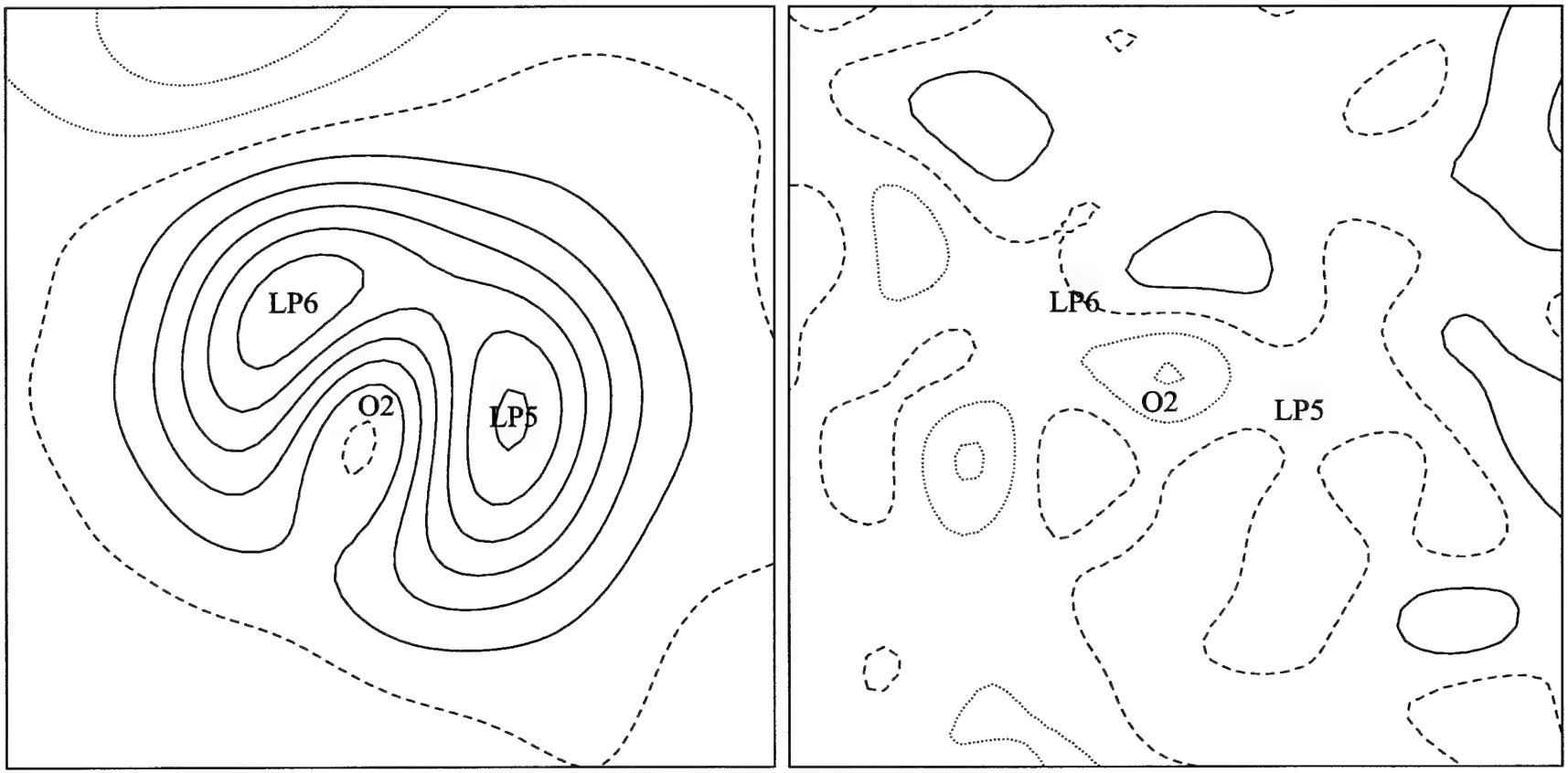

Figure 17. Dynamic model map and residual map in the plane of the lone pairs of O2 of 17β-estradiol•½methanol. Contour intervals are 0.05 eÅ^{-3} with solid lines positive, dashed lines zero, and dotted lines negative.

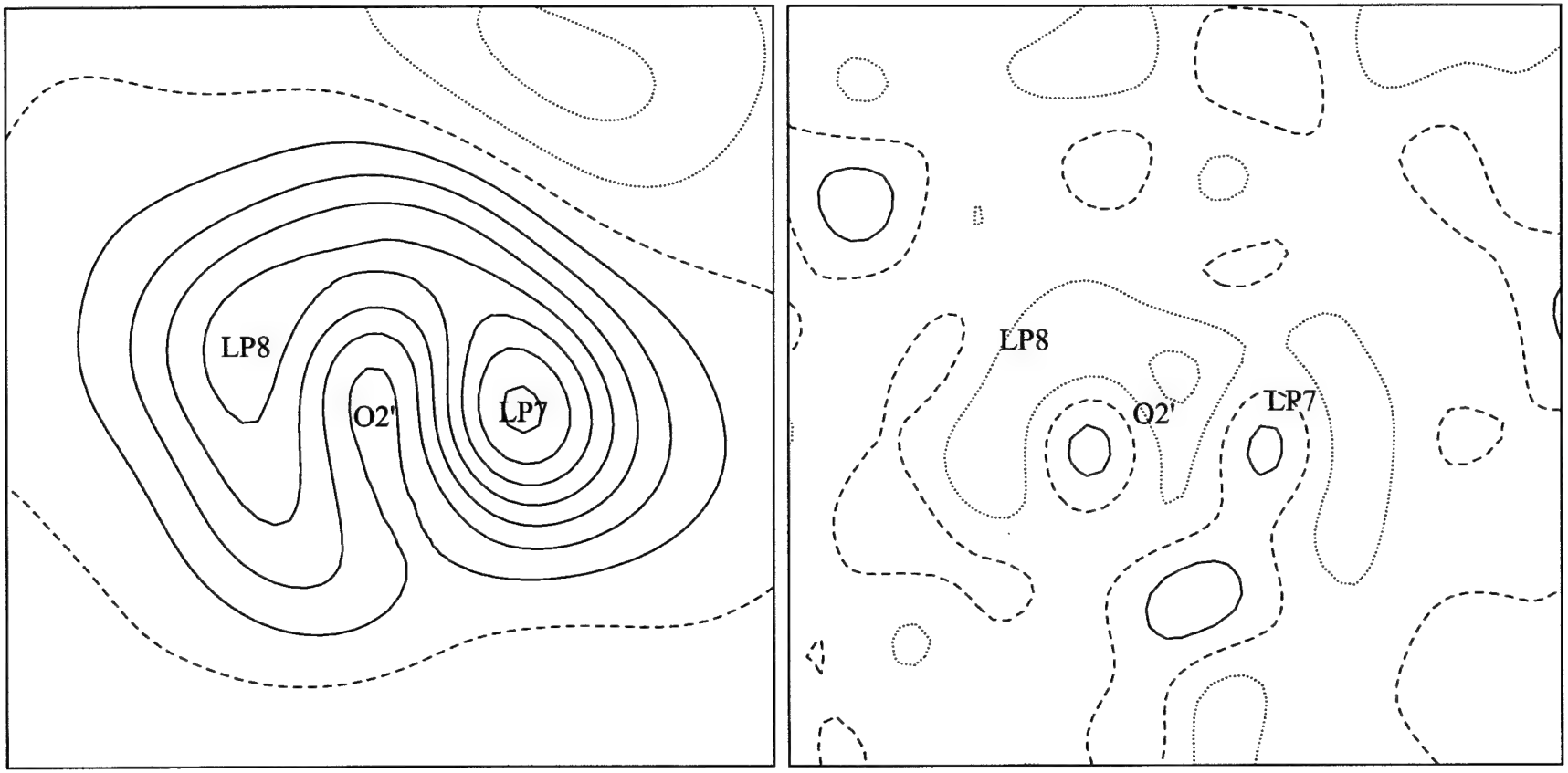

Figure 18. Dynamic model map and residual map in the plane of the lone pairs of O2' of 17β-estradiol•½methanol. Contour intervals are 0.05 e$\AA^{-3}$ with solid lines positive, dashed lines zero, and dotted lines negative.

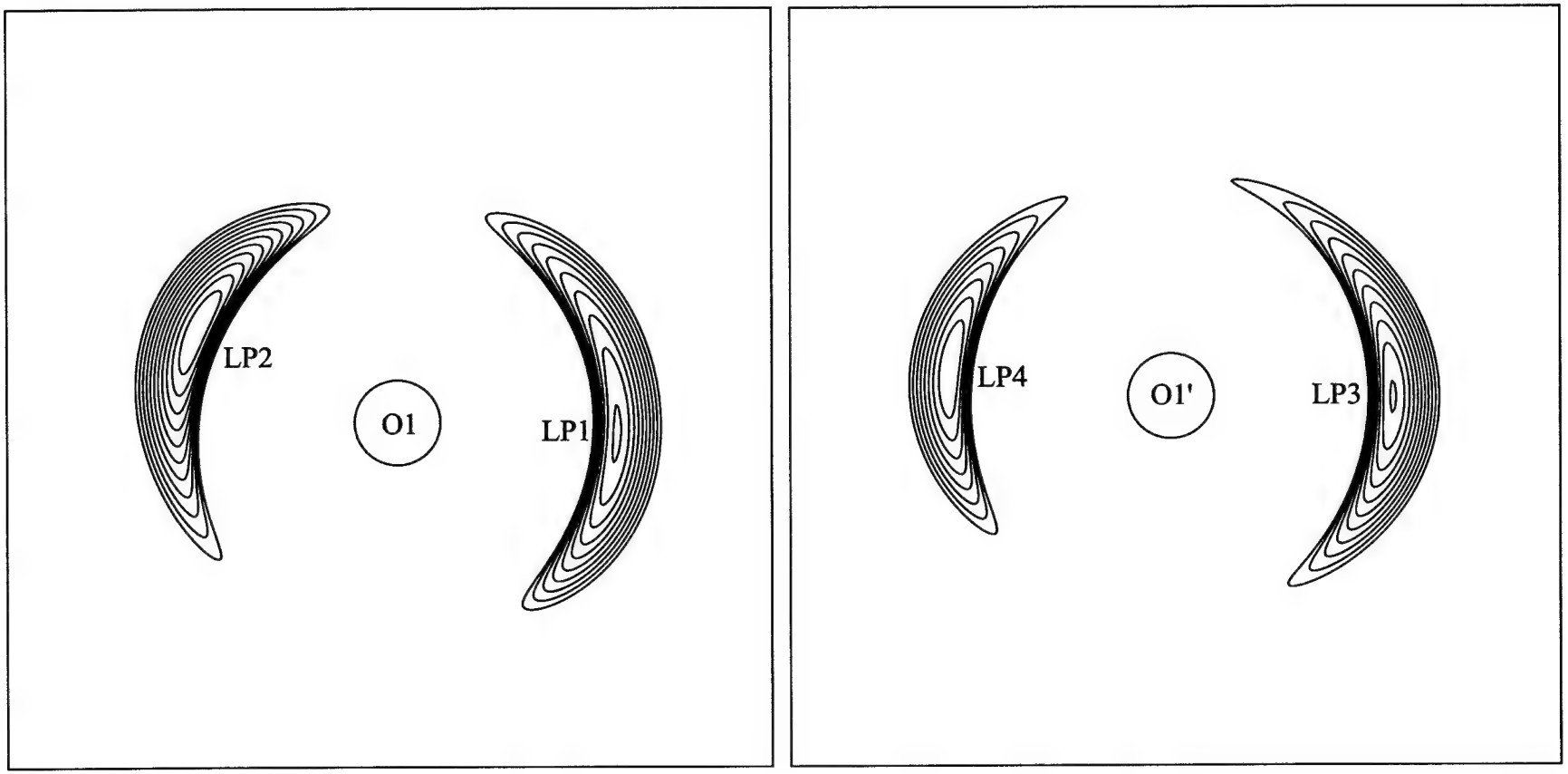

Figure 19. The Laplacian of the total electron density of atoms at rest in the plane of the lone pairs of the O1 and O1' of 17β-estradiol•½methanol. Contour intervals are 5 eÅ^{-5} starting at 80 eÅ^{-5}.

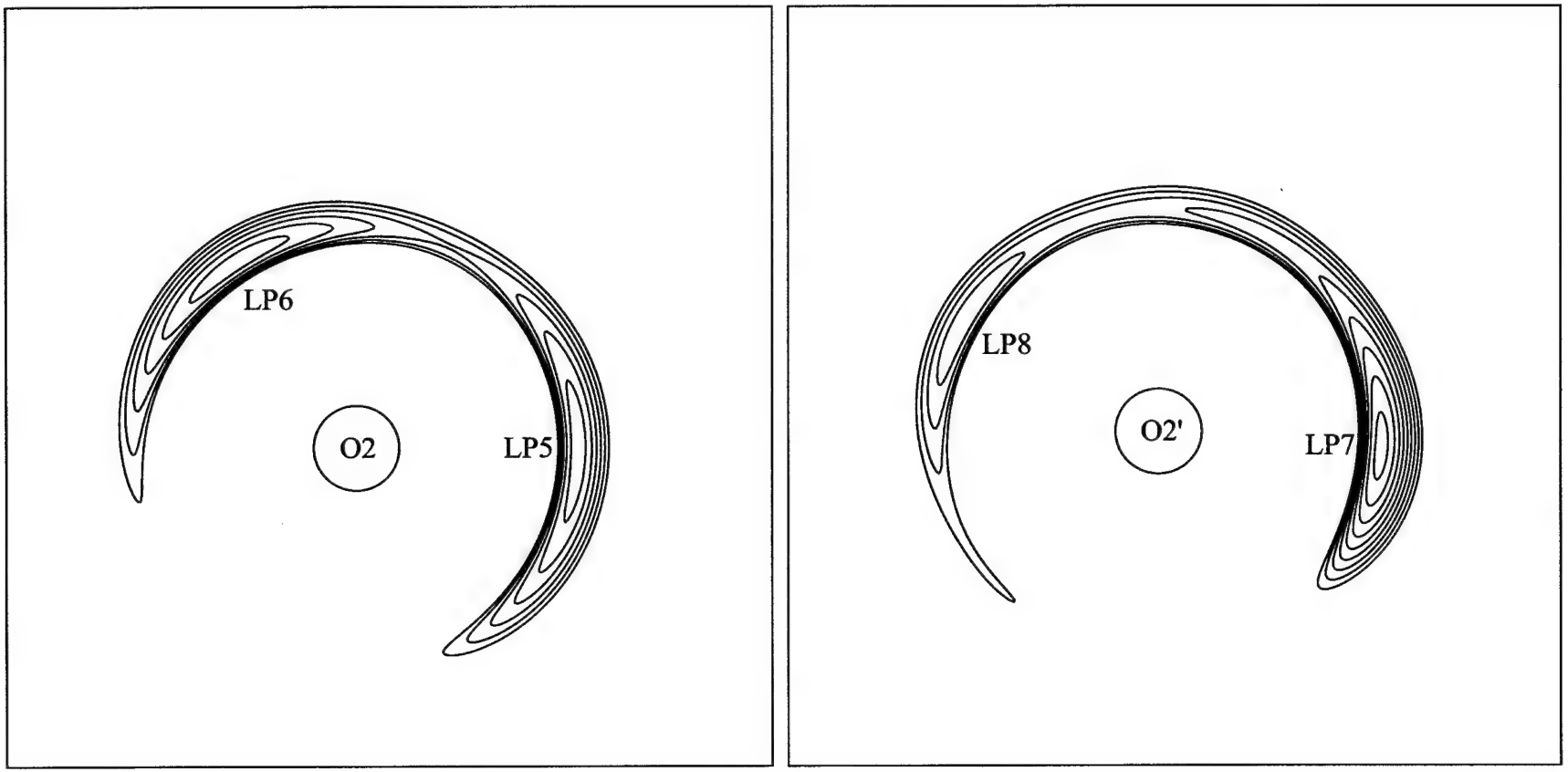

Figure 20. The Laplacian of the total electron density of atoms at rest in the plane of the lone pairs of the O2 and O2' of 17β-estradiol•½methanol. Contour intervals are 5 eÅ^{-5} starting at 90 eÅ^{-5}.

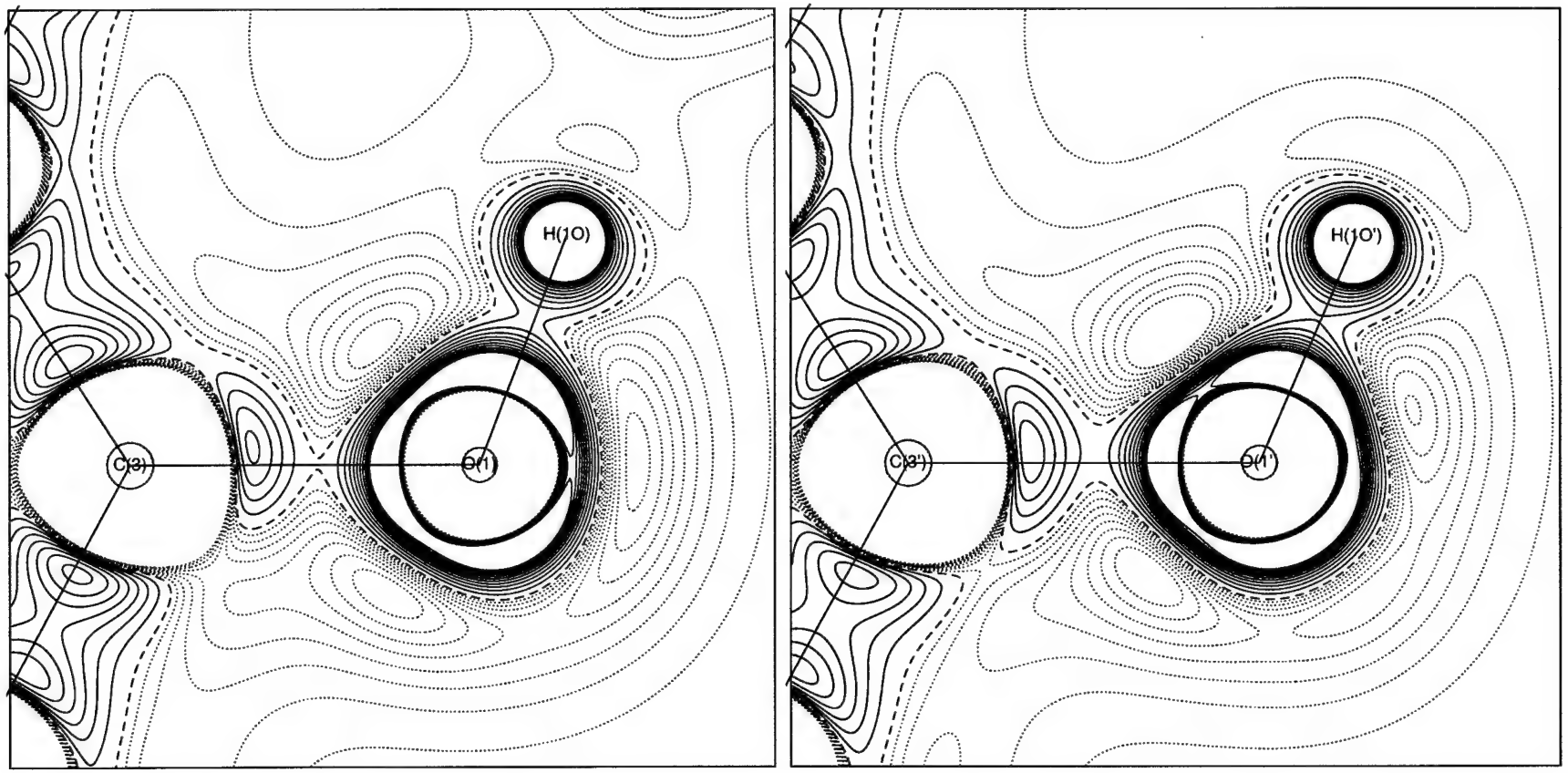

Figure 21. The Laplacian of the total electron density of atoms at rest in the C3–O1–H1O plane and C3'–O1'–H1O' of 17β-estradiol•½methanol. Contour intervals are 5 eÅ^{-5} starting at 5 eÅ^{-5} (solid blue lines), -2 eÅ^{-5} starting at -2 eÅ^{-5} (dotted red lines), and the dashed line plots 0 eÅ^{-5}.

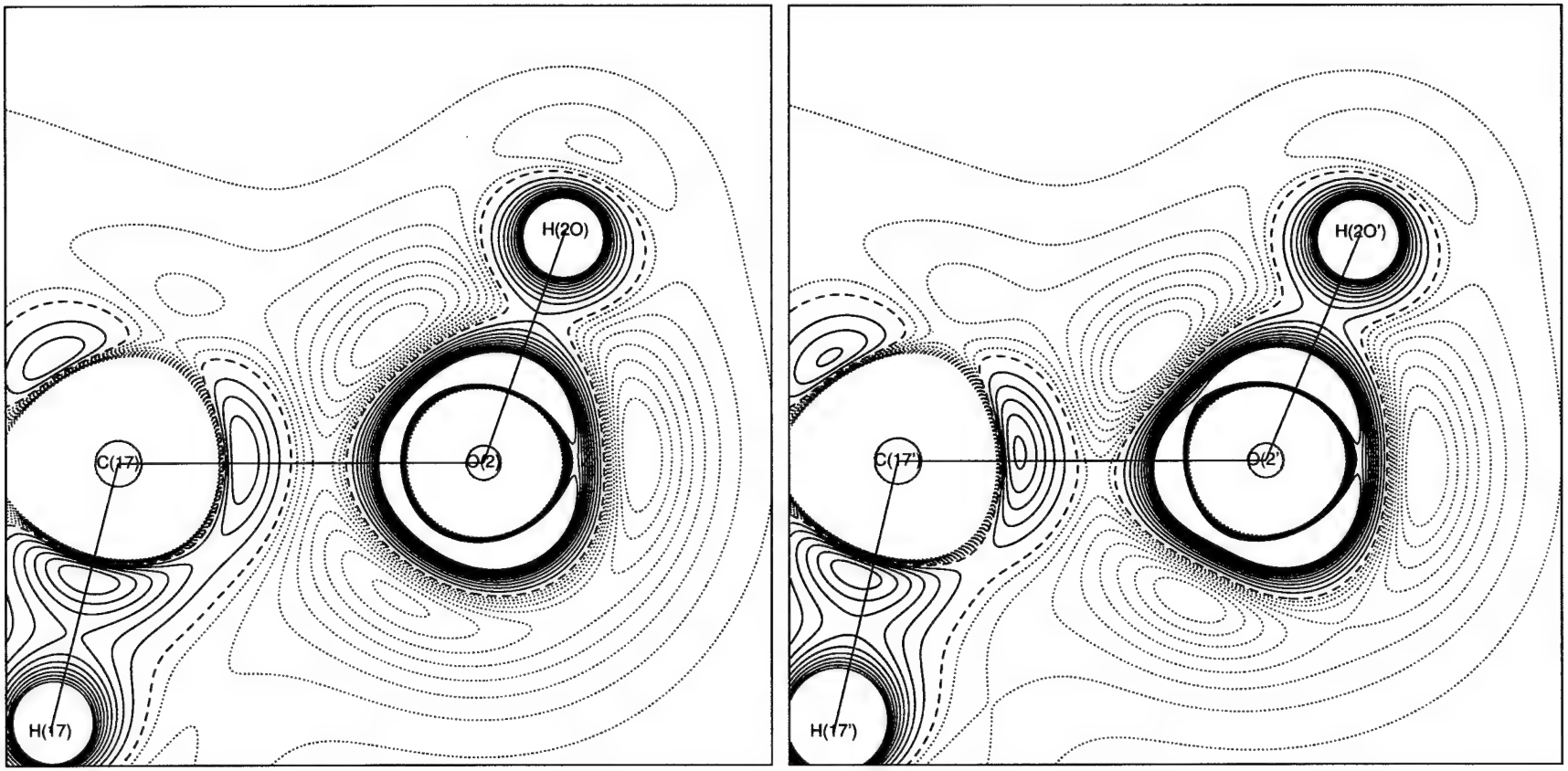

Figure 22. The Laplacian of the total electron density of atoms at rest in the C17–O2–H2O plane and C17'–O2'–H2O' of 17β-estradiol•½methanol. Contour intervals are 5 eÅ^{-5} starting at 5 eÅ^{-5} (solid blue lines), -2 eÅ^{-5} starting at -2 eÅ^{-5} (dotted red lines), and the dashed line plots 0 eÅ^{-5}.

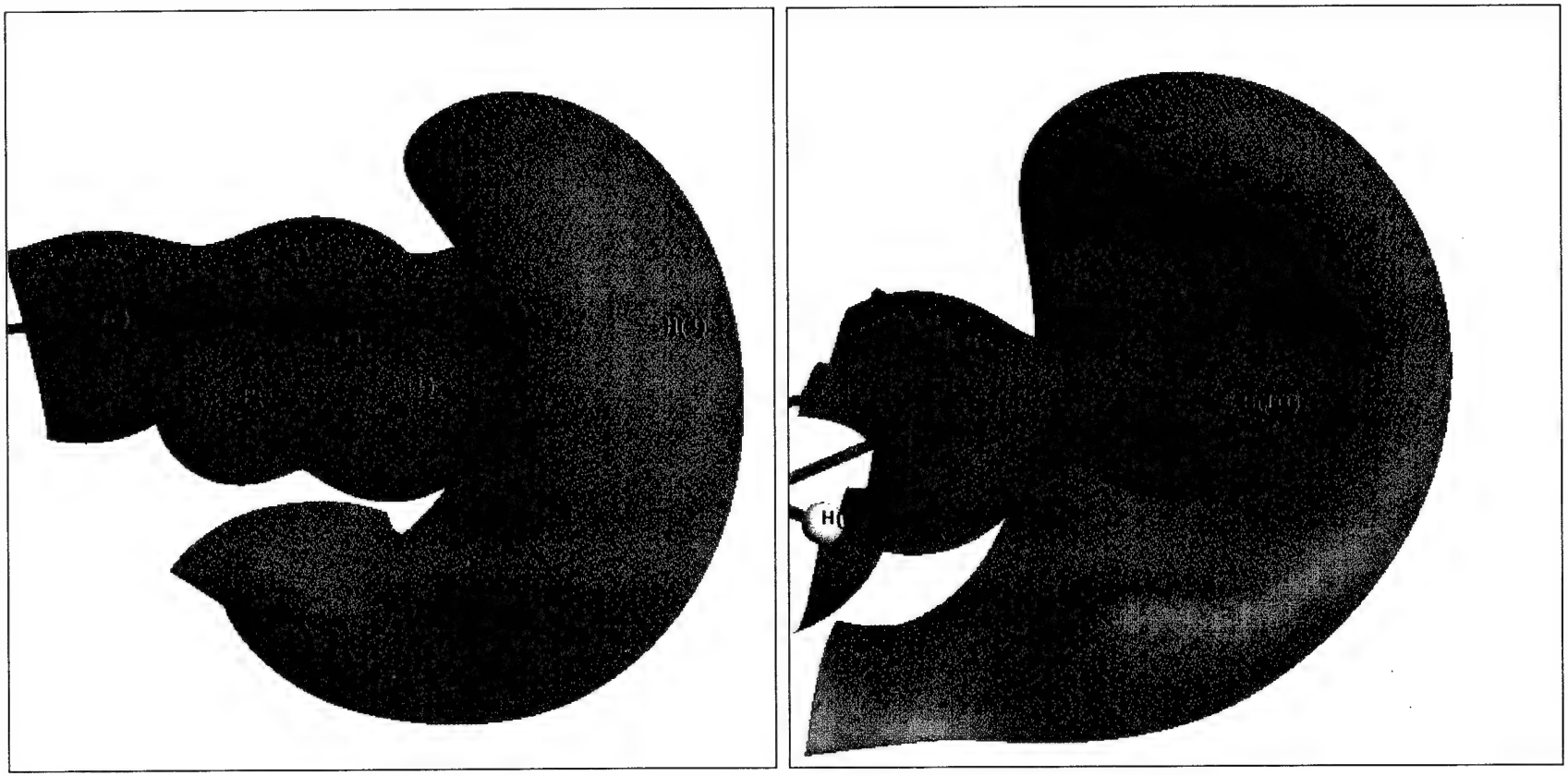

Figure 23. 17β-estradiol•½methanol, molecule 1 C3 hydroxy, red –0.15 eÅ^{-1}, blue 1.0 eÅ^{-1}.

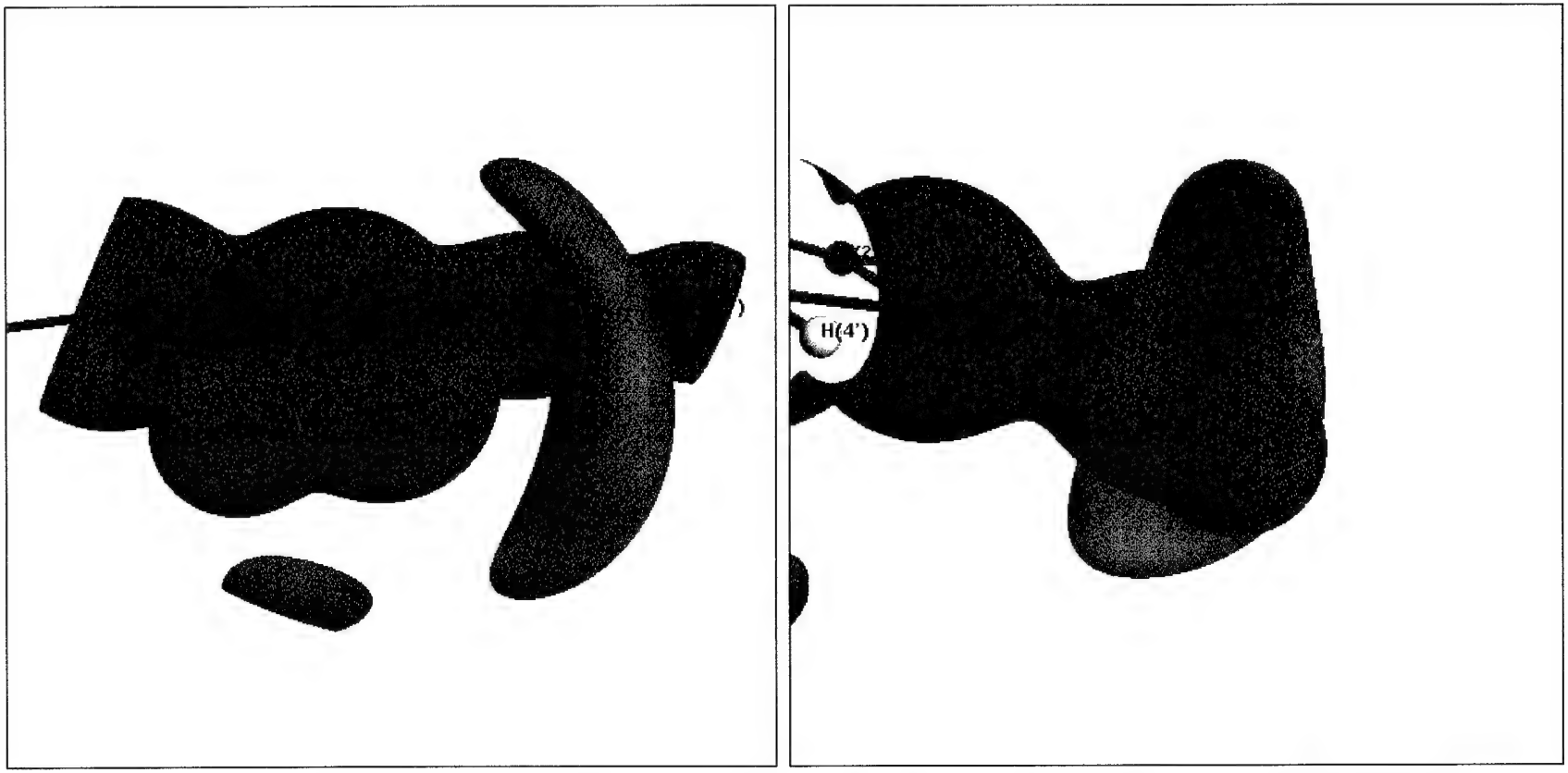

Figure 24. 17β-estradiol•½methanol, molecule 2 C3' hydroxy, red –0.15 eÅ^{-1}, blue 1.0 eÅ^{-1}.

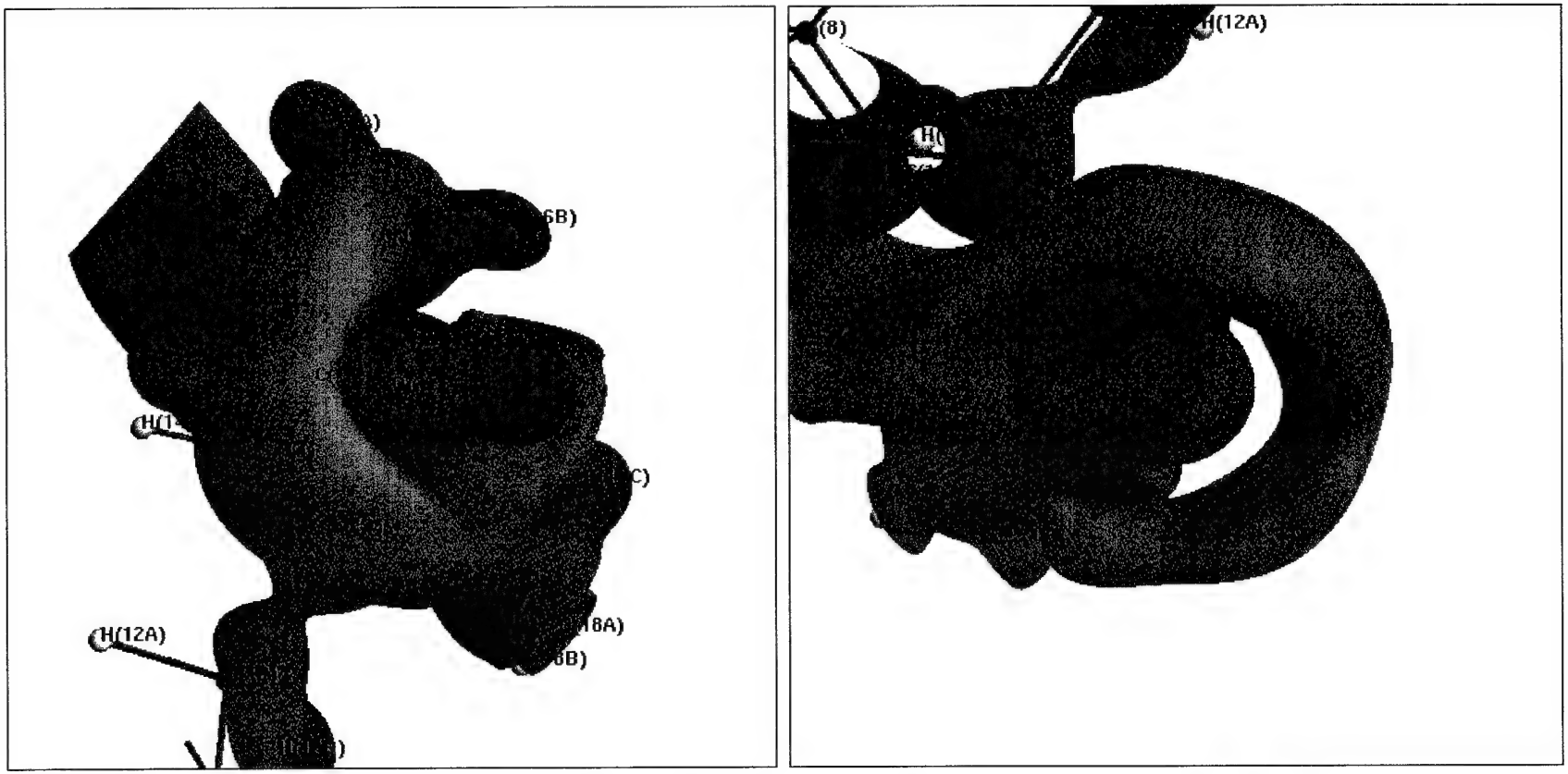

Figure 25. 17β-estradiol•½methanol, molecule 1 C17 hydroxy, red –0.15 eÅ^{-1}, blue 1.0 eÅ^{-1}.

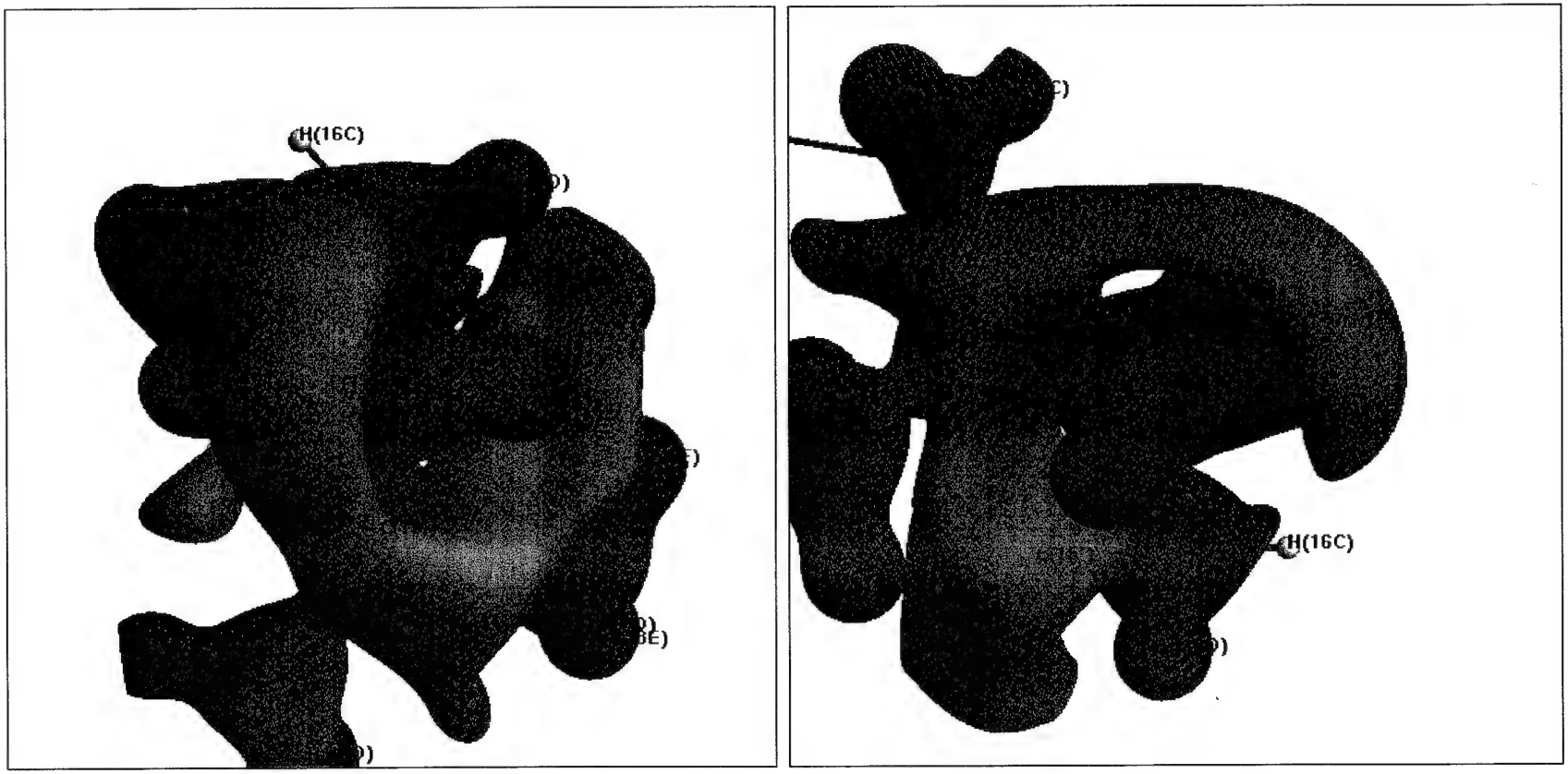

Figure 26. 17β-estradiol•½methanol, molecule 2 C17' hydroxy, red –0.15 eÅ^{-1}, blue 1.0 eÅ^{-1}.

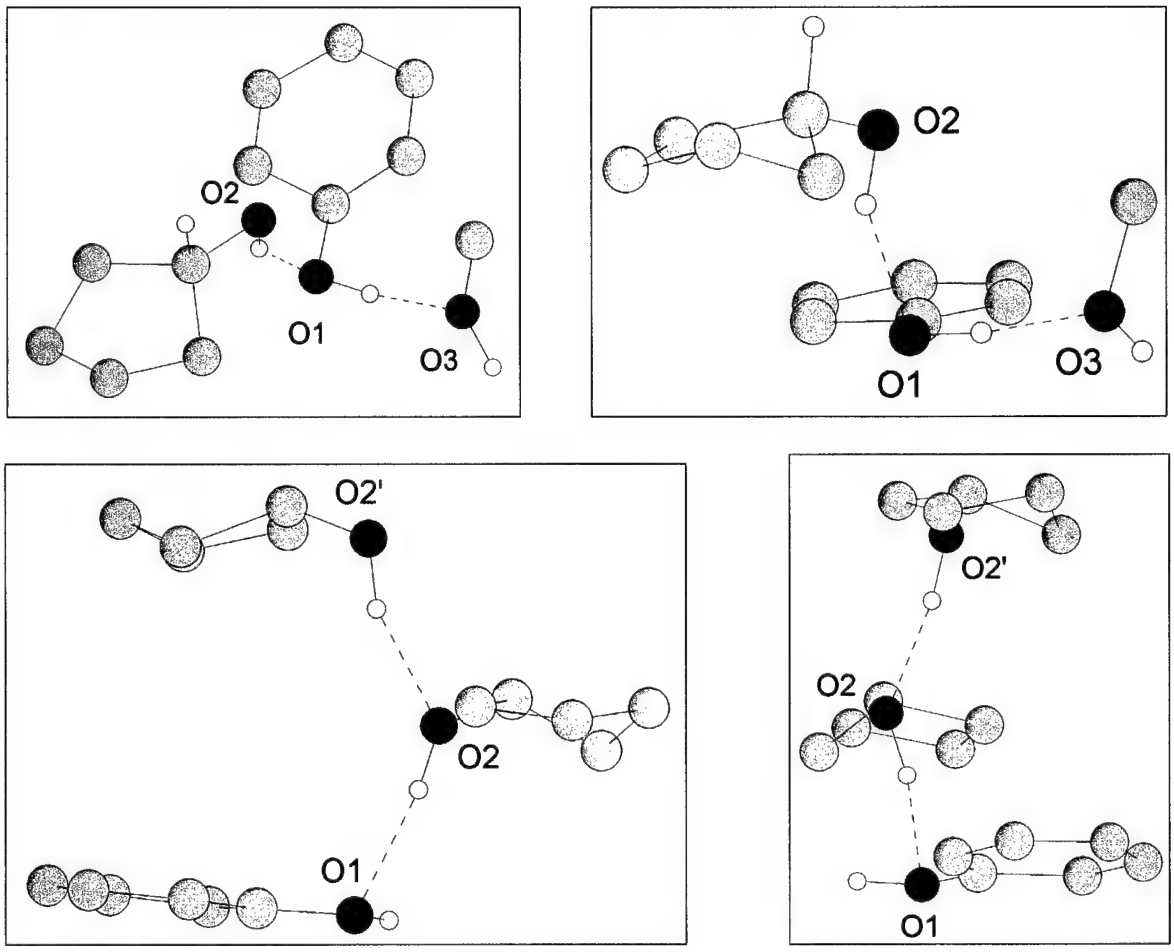

Figure 27. Geometry of hydrogen bonding interactions of molecule 1 of 17β-estradiol•½methanol.

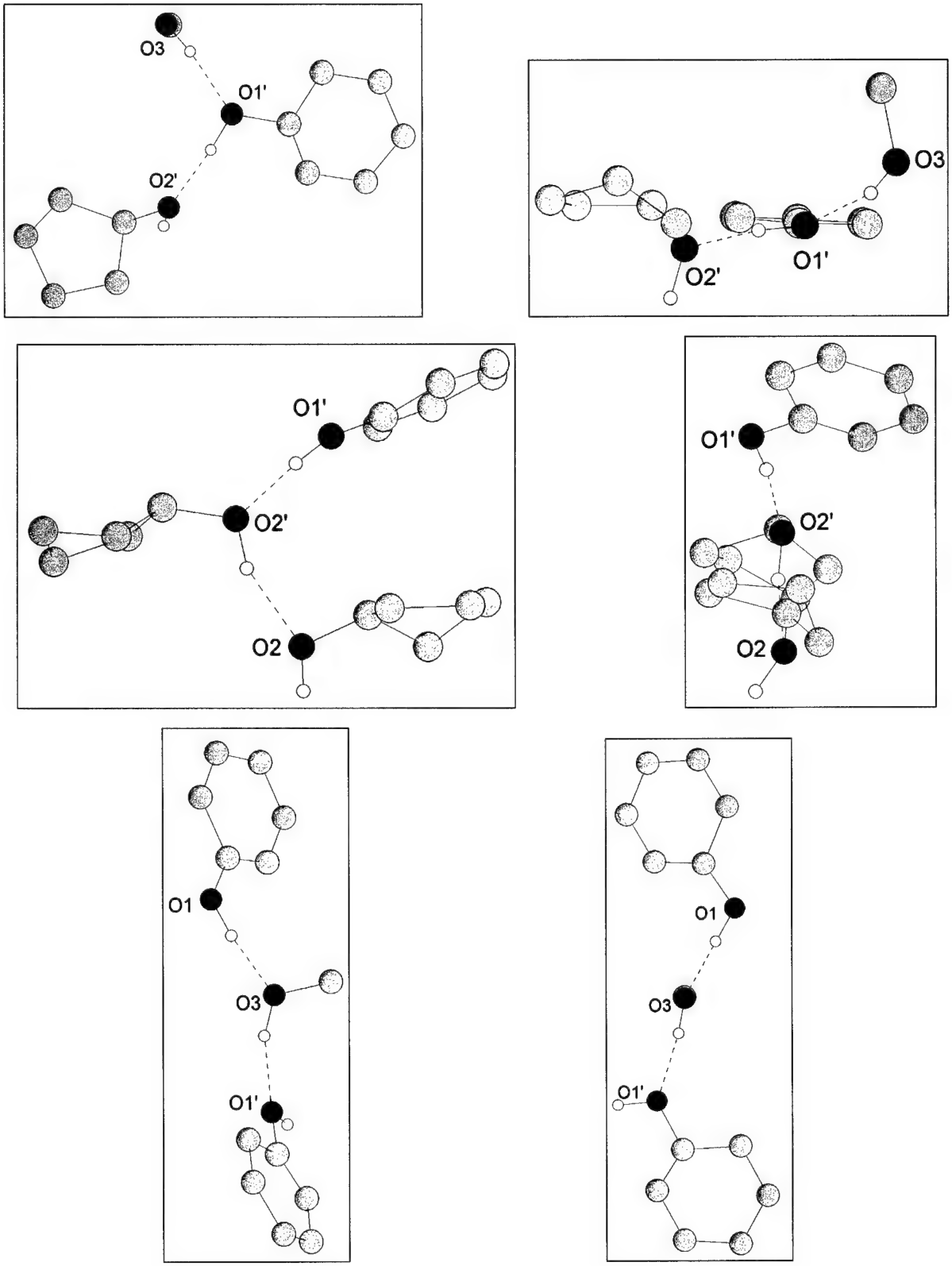

Figure 28. Geometry of hydrogen bonding interactions of molecule 2 and the methanol of 17β-estradiol•½methanol.

Appendix D.

17*a*-estradiol•½H_2O

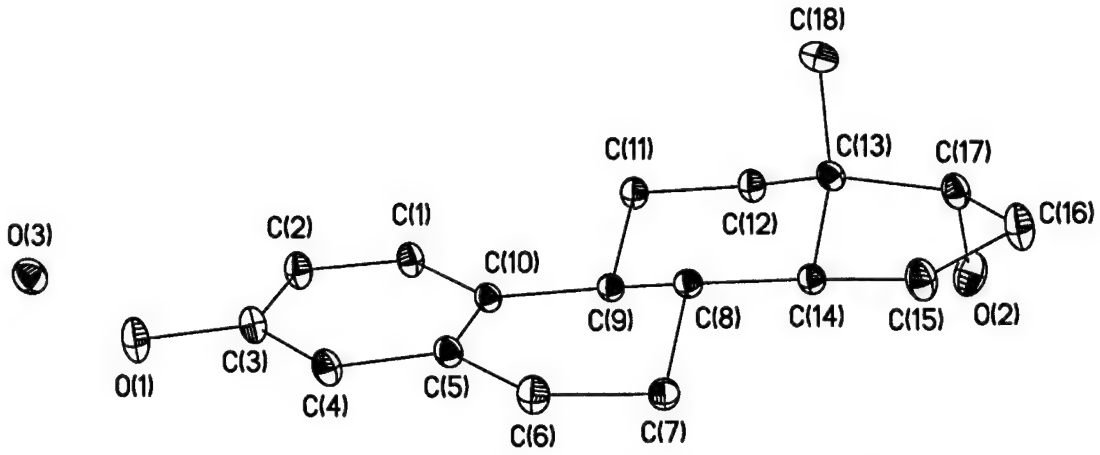

Figure 1. Thermal ellipsoid plot of 17*a*-estradiol•½H_2O where ellipsoids represent 50% probability electron density of the atom. Hydrogen atoms are omitted for clarity.

Run	2θ	ω	ϕ	Scan Width (°)	# of Frames	Frame Times (sec)
1	0	10	0	-0.30	660	96
2	0	10	90	-0.30	660	96
3	0	10	180	-0.30	660	96
4	0	10	270	-0.30	660	96
5	0	10	0	-0.30	100	96
6	-60	-50	45	-0.30	660	180
7	-60	-50	135	-0.30	660	180
8	-60	-50	225	-0.30	660	180
9	-60	-50	315	-0.30	660	180
10	-60	-50	45	-0.30	100	180

Table 1. Data collection parameters for 17*a*-estradiol•½H_2O.

Crystal Data			
Chemical Formula	$C_{18}H_{25}O_{2.5}$		
Temperature	100.0(1) K		
Crystal Dimensions	0.24 x 0.33 x 0.33 mm		
Space Group	C2		
A	19.0235(5) Å		
B	7.0653(2) Å		
C	13.3496(3) Å		
β	124.0544(10)		
Volume	1486.56(10) $Å^3$		
Z (Crystallographic)	4		
Integration Parameters			
	Box Size (°)	Profile Fitting (I/σ)	Simple Sum Perimeter Limit
Low Angle	1.2 x 1.2 x 0.8	40 10	0.02
High Angle	1.0 x 1.0 x 0.6	30 10	0.02
Reflection Statistics (from SORTAV)			
Total Reflections	85540		
Rejected Outliers	69		
Unique Reflections	14593		
Average Redundancy	5.9		
Resolution	1.319 $Å^{-1}$		
Completeness	98.2 %		
R_1	3.76 %		
R_2	4.13 %		
R_w	13.52 %		
Z (Refinement)	1.949		

Table 2. Selected crystal, integration, and reflection data for 17*a*-estradiol•½H_2O.

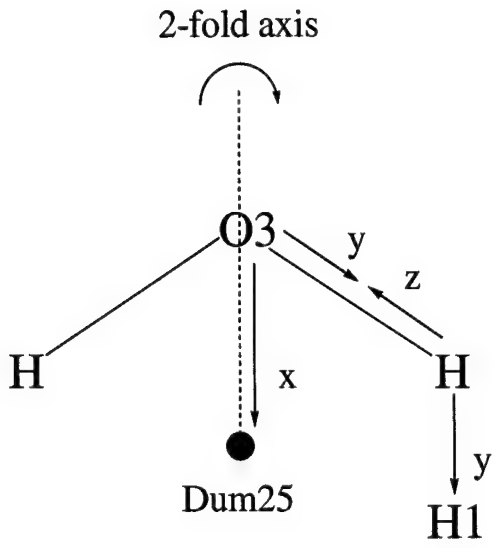

Figure 2. Coordinate system for the water molecule.

	n	m	$\langle n \rangle$	R_1	R_2	R_w	Z	V
Q < -4	0	0	0.0	0.0000	0.0000	0.0000	0.000	0.000
-4 < Q < -3	0	0	0.0	0.0000	0.0000	0.0000	0.000	0.000
-3 < Q < -2	2	1	2.0	0.3784	0.3657	0.3695	1.086	0.381
-2 < Q < -1	43	14	3.1	0.3661	0.4037	0.4846	0.886	0.368
-1 < Q < 0	1161	326	3.6	1.0974	1.1150	1.0573	1.801	3.167
0 < Q < 1	6088	1550	3.9	0.9922	0.9414	0.9133	2.031	1.676
1 < Q < 2	6618	1657	4.0	0.5715	0.5985	0.5448	2.092	0.650
2 < Q < 3	5241	1299	4.0	0.3530	0.4112	0.3720	2.237	0.386
3 < Q < 4	4586	1054	4.4	0.2565	0.3076	0.2699	2.257	0.277
4 < Q < 6	7017	1516	4.6	0.1805	0.2214	0.1905	2.353	0.195
6 < Q < 8	5775	1128	5.1	0.1290	0.1586	0.1406	2.153	0.141
8 < Q < 10	5187	896	5.8	0.0995	0.1227	0.1095	1.999	0.109
10 < Q < 20	17218	2529	6.8	0.0575	0.0728	0.0725	1.645	0.067
20 < Q < 30	16066	1596	10.1	0.0340	0.0467	0.0399	1.227	0.038
30 < Q < 50	10194	745	13.7	0.0244	0.0340	0.0283	1.235	0.027
50 < Q < 100	144	17	8.5	0.0148	0.0164	0.0170	1.048	0.016
100 < Q	0	0	0.0	0.0000	0.0000	0.0000	0.000	0.000

Table 3. Intensity-Significance Intervals where n is the number of reflections, m is the number of unique reflections, $\langle n \rangle$ is the average measurement multiplicity, and Q=I/Max ($\sigma_{int}/\sigma_{ext}$) respectively for 17*a*-estradiol•½H_2O.

	n	m	$\langle n \rangle$	R_1	R_2	R_w	Z	V
D > 1.029	13550	791	17.1	0.0273	0.0387	0.1137	1.986	0.030
1.029 > D > 0.817	13830	774	17.9	0.0329	0.0362	0.1057	1.817	0.039
0.817 > D > 0.713	6005	743	8.1	0.0362	0.0381	0.1209	2.082	0.041
0.713 > D > 0.648	4332	750	5.8	0.0384	0.0368	0.1320	2.145	0.044
0.648 > D > 0.602	4119	748	5.5	0.0480	0.0463	0.1379	2.182	0.053
0.602 > D > 0.566	3914	749	5.2	0.0565	0.0537	0.1396	2.137	0.064
0.566 > D > 0.538	3668	735	5.0	0.0706	0.0660	0.1467	2.076	0.079
0.538 > D > 0.514	3508	729	4.8	0.0891	0.0866	0.1593	2.163	0.100
0.514 > D > 0.495	3483	752	4.6	0.1057	0.1058	0.1609	2.089	0.116
0.495 > D > 0.478	3201	721	4.4	0.1066	0.1015	0.1629	2.055	0.117
0.478 > D > 0.463	3092	720	4.3	0.1054	0.0935	0.1688	2.063	0.114
0.463 > D > 0.449	3023	728	4.2	0.1491	0.1327	0.1945	2.020	0.163
0.449 > D > 0.438	2820	697	4.0	0.1950	0.1897	0.2191	1.970	0.212
0.438 > D > 0.427	2819	720	3.9	0.2140	0.2053	0.2331	1.947	0.236
0.427 > D > 0.417	2608	686	3.8	0.2517	0.2218	0.2650	2.007	0.280
0.417 > D > 0.408	2594	700	3.7	0.2849	0.2656	0.2784	1.927	0.320
0.408 > D > 0.400	2537	712	3.6	0.3111	0.2877	0.3036	1.932	0.351
0.400 > D > 0.393	2331	678	3.4	0.3549	0.3364	0.3461	1.926	0.405
0.393 > D > 0.386	2277	682	3.3	0.3852	0.3783	0.3658	1.941	0.431
0.386 > D > 0.379	1629	513	3.2	0.4653	0.4655	0.4370	1.769	0.540

Table 4. Equal-Volume Resolution Shells where n is the number of reflections, m is the number of unique reflections, $\langle n \rangle$ is the average measurement multiplicity, and D=sinθ/λ (Å^{-1}) respectively for 17*a*-estradiol•½H_2O.

	Monopole	sp^2		sp^3
		20	33+	32-
O1	-0.50			
O2	-0.49			
C1	-0.30	-0.22	0.34	
C2	-0.38	-0.19	0.37	
C3	0.27	-0.21	0.38	
C4	-0.33	-0.17	0.36	
C5	-0.18	-0.22	0.33	
C6	-0.26			0.31
C7	-0.31			0.34
C8	-0.21			0.39
C9	-0.17			0.31
C10	-0.25	-0.18	0.37	
C11	-0.31			0.35
C12	-0.28			0.31
C13	-0.16			0.38
C14	-0.20			0.38
C15	-0.26			0.33
C16	-0.35			0.42
C17	0.20			0.38
C18	-0.32			0.27

	Monopole
H1O	0.40
H2O	0.38
H1	0.23
H2	0.22
H4	0.26
H6x	0.20
H7x	0.17
H8	0.20
H9	0.16
H11x	0.17
H12x	0.16
H14	0.19
H15x	0.16
H16x	0.18
H17	0.13
H18x	0.18

Atoms	Kappa	κ	κ'
O1, O2	1	0.97	1.16
C3	2	1.01	0.92
C17	3	1.02	0.95
C1, C2, C4	4	0.97	0.92
C5, C10	5	0.98	0.87
C6, C7, C8, C9, C11, C12, C13, C14, C15, C16, C17, C18	6	0.98	0.95
all C-H hydrogen atoms	7	1.20	1.29
H1O, H2O	8	1.20	1.29
O3	9		
H3O	10		

Table 5. Starting values entered into the model for the multipole refinement for 17*a*-estradiol•½H_2O. Units for multipole populations are e^-.

Atom	X	Y	Z
O1	0.11679(1)	0.53051(6)	-0.40619(2)
O2	0.59212(2)	0.40154(6)	0.50812(2)
C1	0.25908(2)	0.32552(6)	-0.10524(2)
C2	0.19311(2)	0.34213(6)	-0.22673(3)
C3	0.18285(2)	0.51139(6)	-0.28726(2)
C4	0.24011(2)	0.65930(6)	-0.22661(2)
C5	0.30786(2)	0.64004(6)	-0.10514(2)
C6	0.37135 (2)	0.80070(6)	-0.04731(3)
C7	0.43341(2)	0.78376(6)	0.08978(2)
C8	0.46397(2)	0.58022(6)	0.12773(2)
C9	0.38729(2)	0.45262(6)	0.09205(2)
C10	0.31740(2)	0.47201(6)	-0.04185(2)
C11	0.41421(2)	0.24647(6)	0.13289(2)
C12	0.48474(2)	0.23044(6)	0.26845(2)
C13	0.56071(2)	0.35552(6)	0.30229(2)
C14	0.52936(2)	0.56082(6)	0.26359(2)
C15	0.61131(2)	0.67896(6)	0.32646(3)
C16	0.67369(2)	0.56827(7)	0.44502(3)
C17	0.62831(2)	0.38263(7)	0.43874(3)
C18	0.60695(2)	0.27766(7)	0.24600(3)
O3	0.00000	0.23142(6)	-0.50000

Atom	X	Y	Z
H1O	0.0858(5)	0.4125(12)	-0.4373(7)
H2O	0.5776(5)	0.2772(12)	0.5221(7)
H1	0.2662(4)	0.1964(10)	-0.0571(6)
H2	0.1501(4)	0.2251(10)	-0.2723(5)
H4	0.2325(4)	0.7893(9)	-0.2743(5)
H6A	0.3381(4)	0.9357(10)	-0.0691(6)
H6B	0.4076(3)	0.7980(8)	-0.0879(5)
H7A	0.4029(3)	0.8300(8)	0.1345(5)
H7B	0.4877(4)	0.8759(9)	0.1198(5)
H8	0.4908(3)	0.5308(8)	0.0777(5)
H9	0.3621(3)	0.5067(8)	0.1432(5)
H11A	0.3595(3)	0.1651(8)	0.1144(4)
H11B	0.4347(3)	0.1816(9)	0.0792(5)
H12A	0.4574(3)	0.2717(8)	0.3184(5)
H12B	0.5030(3)	0.0821(8)	0.2897(5)
H14	0.4967(3)	0.5946(8)	0.3080(5)
H15A	0.6023(4)	0.8213(9)	0.3488(5)
H15B	0.6368(4)	0.6833(10)	0.2710(6)
H16A	0.6891(4)	0.6405(10)	0.5271(6)
H16B	0.7310(4)	0.5301(10)	0.4497(6)
H17	0.6733(3)	0.2639(8)	0.4791(4)
H18A	0.6315(4)	0.1412(9)	0.2813(6)
H18B	0.6599(4)	0.3615(11)	0.2676(6)
H18C	0.5672(4)	0.2631(10)	0.1507(5)
H3O	-0.0329(6)	0.1294(14)	-0.4989(8)

Table 6. Fractional atomic coordinates for 17*a*-estradiol•½H_2O.

Atom	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.01474(8)	0.01787(9)	0.01159(8)	-0.00278(7)	0.00232(7)	0.00226(7)
O2	0.02309(10)	0.02411(11)	0.01353(9)	-0.00461(9)	0.00994(8)	-0.00101(8)
C1	0.01204(9)	0.01148(9)	0.01149(9)	-0.00201(7)	0.00414(8)	0.00130(7)
C2	0.01229(9)	0.01414(10)	0.01165(9)	-0.00233(8)	0.00411(8)	0.00150(8)
C3	0.01088(9)	0.01535(10)	0.01028(9)	-0.00064(7)	0.00421(7)	0.00195(8)
C4	0.01196(9)	0.01291(9)	0.01167(9)	0.00007(7)	0.00481(8)	0.00282(7)
C5	0.01117(8)	0.00945(8)	0.01079(8)	0.00050(7)	0.00505(7)	0.00167(7)
C6	0.01588(10)	0.00952(8)	0.01253(9)	-0.00106(7)	0.00521(8)	0.00213(7)
C7	0.01282(9)	0.00788(8)	0.01220(9)	-0.00003(7)	0.00565(8)	0.00038(7)
C8	0.01065(8)	0.00806(7)	0.01068(8)	0.00034(6)	0.00579(7)	0.00082(6)
C9	0.01013(8)	0.00851(8)	0.01017(8)	0.00023(6)	0.00513(7)	0.00084(6)
C10	0.01026(8)	0.00922(8)	0.01016(8)	0.00013(6)	0.00499(7)	0.00115(6)
C11	0.01317(9)	0.00837(8)	0.01196(9)	-0.00036(7)	0.00511(8)	0.00119(7)
C12	0.01257(9)	0.01020(8)	0.01198(9)	-0.00066(7)	0.00537(8)	0.00224(7)
C13	0.01036(8)	0.01021(8)	0.01170(9)	0.00115(7)	0.00540(7)	0.00168(7)
C14	0.01012(8)	0.00939(8)	0.01077(8)	-0.00013(6)	0.00488(7)	0.00063(7)
C15	0.01293(9)	0.01331(10)	0.01594(10)	-0.00301(8)	0.00472(8)	0.00240(8)
C16	0.01292(10)	0.01801(11)	0.01616(11)	-0.00385(9)	0.00231(9)	0.00290(9)
C17	0.01204(9)	0.01325(9)	0.01289(9)	0.00060(7)	0.00418(8)	0.00286(8)
C18	0.01651(11)	0.01638(11)	0.02061(12)	0.00425(9)	0.01234(10)	0.00207(9)
O3	0.01581(12)	0.01773(13)	0.02136(14)	0.00000	0.00928(11)	0.00000

Table 7. Anisotropic thermal parameters of non-H atoms for 17*a*-estradiol•½H_2O.

Atom	U_{iso}
H1O	0.0386(18)
H2O	0.0471(20)
H1	0.0519(16)
H2	0.0460(14)
H4	0.0447(14)
H6A	0.0564(15)
H6B	0.0449(13)
H7A	0.0413(13)
H7B	0.0434(12)
H8	0.0380(12)
H9	0.0392(12)
H11A	0.0436(13)
H11B	0.0464(13)
H12A	0.0410(12)
H12B	0.0445(13)

Atom	U_{iso}
H14	0.0407(12)
H15A	0.0470(13)
H15B	0.0550(15)
H16A	0.0586(16)
H16B	0.0598(16)
H17	0.0426(12)
H18A	0.0577(15)
H18B	0.0644(17)
H18C	0.0538(14)
H3O	0.1065(51)

Table 8. Isotropic thermal parameters of H atoms for 17*a*-estradiol•½H_2O.

Atoms	Bond Length (Å)
O1 – C3	1.3724(3)
O2 – C17	1.4365(4)
C1 – C2	1.3927(4)
C1 – C10	1.4024(4)
C2 – C3	1.3945(4)
C3 – C4	1.3951(4)
C4 – C5	1.4030(3)
C5 – C6	1.5162(4)
C5 – C10	1.4087(3)
C6 – C7	1.5289(4)
C7 – C8	1.5274(3)
C8 – C9	1.5457(3)
C8 – C14	1.5261(3)

Atoms	Bond Length (Å)
C9 – C10	1.5232(3)
C9 – C11	1.5390(3)
C11 – C12	1.5390(4)
C12 – C13	1.5305(4)
C13 – C14	1.5432(3)
C13 – C17	1.5444(4)
C13 – C18	1.5431(4)
C14 – C15	1.5382(4)
C15 – C16	1.5560(4)
C16 – C17	1.5465(4)

Table 9. Bond distances of non-H atoms of 17*a*-estradiol•½H_2O.

Atoms	Bond Angle (°)
C3 – O1 – H1O	110.8(5)
C17 – O2 – H2O	109.3(5)
C2 – C1 – C10	122.2(1)
C2 – C1 – H1	119.7(4)
C10 – C1 – H1	118.1(4)
C1 – C2 – C3	119.3(1)
C1 – C2 – H2	119.7(4)
C3 – C2 – H2	120.9(4)
O1 – C3 – C2	119.7(1)
O1 – C3 – C4	120.6(1)
C2 – C3 – C4	119.7(1)
C3 – C4 – C5	120.8(1)
C3 – C4 – H4	119.5(4)
C5 – C4 – H4	119.8(4)
C4 – C5 – C6	118.0(1)
C4 – C5 – C10	120.1(1)
C6 – C5 – C10	121.8(1)
C5 – C6 - C7	114.3(1)
C5 – C6 – H6A	110.0(4)
C5 – C6 – H6B	106.2(3)
C7 – C6 – H6A	109.3(4)
C7 – C6 – H6B	108.3(3)
H6A – C6 – H6B	108.5(5)
C6 – C7 – C8	111.5(1)
C6 – C7 – H7A	109.9(3)
C6 – C7 – H7B	109.3(3)
C8 – C7 – H7A	108.7(3)
C8 – C7 – H7B	109.5(4)
H7A – C7 – H7B	107.8(4)
C7 – C8 – C9	109.2(1)
C7 – C8 – C14	112.6(1)

Atoms	Bond Angle (°)
C9 – C8 – C14	108.3(1)
C7 – C8 – H8	108.5(4)
C9 – C8 – H8	107.8(3)
C14 – C8 – H8	110.3(3)
C8 – C9 – C10	111.2(1)
C8 – C9 – C11	111.9(1)
C10 – C9 – C11	113.5(1)
C8 – C9 – H9	105.7(3)
C10 – C9 – H9	107.5(3)
C11 – C9 – H9	106.4(4)
C1 – C10 – C5	117.9(1)
C1 – C10 – C9	121.2(1)
C5 – C10 – C9	120.9(1)
C9 – C11 – C12	112.6(1)
C9 – C11 – H11A	109.4(3)
C9 – C11 – H11B	109.6(4)
C12 – C11 – H11A	108.7(3)
C12 – C11 – H11B	110.2(3)
H11A – C11 – H11B	106.1(5)
C11 – C12 – C13	111.2(1)
C11 – C12 – H12A	107.4(3)
C11 – C12 – H12B	108.5(3)
C13 – C12 – H12A	111.1(3)
C13 – C12 – H12B	111.6(3)
H12A – C12 – H12B	106.8(5)
C12 – C13 – C14	108.7(1)
C12 – C13 – C17	116.4(1)
C12 – C13 – C18	110.6(1)
C14 – C13 – C17	100.9(1)
C14 – C13 – C18	113.0(1)
C17 – C13 – C18	107.1(1)

Atoms	Bond Angle (°)
C8 – C14 – C13	112.8(1)
C8 – C14 – C15	120.2(1)
C13 – C14 – C15	104.1(1)
C8 – C14 – H14	106.9(3)
C13 – C14 – H14	104.6(3)
C15 – C14 – H14	107.1(3)
C14 – C15 – C16	104.2(1)
C14 – C15 – H15A	112.5(3)
C14 – C15 – H15B	110.2(4)
C16 – C15 – H15A	109.4(3)
C16 – C15 – H15B	109.2(4)
H15A – C15 – H15B	111.0(5)
C15 – C16 – C17	106.7(1)
C15 – C16 – H16A	114.2(4)
C15 – C16 – H16B	110.6(4)
C17 – C16 – H16A	106.2(4)
C17 – C16 – H16B	107.6(4)
H16A – C16 – H16B	111.1(5)
O2 – C17 – C13	112.9(1)
O2 – C17 – C16	109.9(1)
C13 – C17 – C16	103.9(1)
O2 – C17 – H17	106.1(3)
C13 – C17 – H17	112.9(3)
C16 – C17 – H17	111.3(3)
C13 – C18 – H18A	109.8(4)
C13 – C18 – H18B	112.5(4)
C13 – C18 – H18C	113.7(4)
H18A – C18 – H18B	105.8(6)
H18A – C18 – H18C	106.6(6)
H18B – C18 – H18C	108.1(5)
H3O – O3 – H3O'	82.7(10)

Table 10. Bond angles of 17*a*-estradiol•½H_2O.

Atom	Monopole Population ($P_{0,0}$)
O1	6.519(12)
O2	6.526(12)
C1	4.222(23)
C2	4.254(22)
C3	3.855(20)
C4	4.247(22)
C5	4.127(21)
C6	4.217(22)
C7	4.217(21)
C8	4.127(21)
C9	4.122(21)
C10	4.101(21)
C11	4.226(20)
C12	4.236(20)
C13	4.189(22)
C14	4.121(22)
C15	4.308(21)
C16	4.302(21)
C17	3.849(19)
C18	4.379(22)
O3	3.274(8)

Atom	Monopole Population ($P_{0,0}$)
H1O	0.621(11)
H2O	0.611(11)
H1	0.780(11)
H2	0.788(10)
H4	0.783(11)
H6A	0.853(9)
H6B	0.853(9)
H7A	0.854(7)
H7B	0.854(7)
H8	0.818(10)
H9	0.821(10)
H11A	0.858(8)
H11B	0.858(8)
H12A	0.852(8)
H12B	0.852(8)
H14	0.844(11)
H15A	0.853(8)
H15B	0.853(8)
H16A	0.851(9)
H16B	0.851(9)
H17	0.908(10)
H18A	0.879(7)
H18B	0.879(7)
H18C	0.879(7)
H3O	0.726(8)

Table 11. Monopole populations (e^-) of 17*a*-estradiol•½H_2O.

Multipoles	O1	O2	O3
$P_{1,+1}$	-0.011(7)	-0.036(7)	0.0
$P_{1,-1}$	0.020(11)	0.030(11)	0.048(10)
$P_{1,0}$	0.029(8)	0.014(6)	0.0
$P_{2,0}$	0.096(7)	0.083(7)	0.0
$P_{2,+1}$	-0.037(6)	-0.016(6)	0.0
$P_{2,-1}$	-0.035(7)	-0.046(7)	0.0
$P_{2,+2}$	-0.064(7)	-0.021(7)	0.0
$P_{2,-2}$	0.022(7)	0.065(7)	0.0
$P_{3,0}$	0.014(12)	-0.040(9)	0.0
$P_{3,+1}$	-0.015(9)	-0.081(8)	0.0
$P_{3,-1}$	0.029(12)	-0.017(13)	0.0
$P_{3,+2}$	0.026(10)	-0.016(9)	0.0
$P_{3,-2}$	0.022(11)	0.089(13)	0.0
$P_{3,+3}$	0.124(8)	0.077(9)	-0.100(7)
$P_{3,-3}$	0.020(11)	-0.042(14)	0.0
$P_{4,0}$	0.0	-0.080(11)	0.0
$P_{4,+1}$	0.0	0.034(10)	0.0
$P_{4,-1}$	0.0	0.0	0.0
$P_{4,+2}$	0.0	0.011(10)	0.0
$P_{4,-2}$	-0.018(10)	0.021(11)	0.0
$P_{4,+3}$	-0.062(10)	0.032(10)	0.0
$P_{4,-3}$	0.0	0.047(11)	0.0
$P_{4,+4}$	0.018(9)	-0.023(10)	-0.059(6)
$P_{4,-4}$	-0.090(10)	-0.071(11)	0.0

Table 12. Multipole populations (e^-) of Oxygen and Nitrogen atoms of 17*a*-estradiol•½H_2O.

Multipoles	C1	C2	C3	C4	C5	C6	C7	C8	C9
$P_{1,+1}$	-0.048(11)	-0.153(16)	-0.089(14)	0.047(12)	0.186(16)	0.114(15)	0.108(14)	-0.019(11)	-0.021(11)
$P_{1,-1}$	-0.074(16)	-0.041(13)	0.155(13)	0.172(17)	0.104(13)	0.0	-0.027(11)	-0.131(13)	0.122(14)
$P_{1,0}$	0.073(11)	0.075(11)	0.091(12)	0.064(11)	0.0	0.023(11)	-0.119(12)	-0.103(13)	0.0
$P_{2,0}$	-0.242(9)	-0.175(10)	-0.226(9)	-0.171(10)	-0.250(10)	-0.021(9)	-0.028(9)	0.039(9)	0.0
$P_{2,+1}$	0.035(9)	0.066(10)	-0.017(10)	0.0	0.0	-0.010(9)	0.023(9)	-0.018(9)	0.0
$P_{2,-1}$	0.0	0.0	-0.039(9)	-0.011(10)	0.012(9)	0.038(9)	0.0	0.0	0.018(8)
$P_{2,+2}$	0.011(10)	0.035(10)	0.067(11)	0.0	0.031(11)	0.0	0.036(8)	-0.027(8)	0.017(8)
$P_{2,-2}$	-0.063(10)	-0.055(10)	-0.013(10)	-0.055(11)	-0.018(11)	-0.069(9)	0.010(9)	0.029(9)	0.0
$P_{3,0}$	-0.050(17)	-0.026(16)	-0.070(17)	-0.064(16)	0.0	-0.018(16)	0.0	0.103(14)	0.223(15)
$P_{3,+1}$	0.0	0.0	0.060(13)	0.0	0.023(14)	-0.085(12)	-0.085(12)	0.054(15)	0.105(14)
$P_{3,-1}$	0.022(14)	-0.019(13)	0.044(13)	-0.027(13)	0.015(14)	-0.046(13)	0.096(13)	0.124(15)	0.128(12)
$P_{3,+2}$	0.029(15)	0.0	-0.050(16)	0.019(14)	0.0	0.048(15)	-0.029(14)	-0.187(15)	0.025(15)
$P_{3,-2}$	0.018(14)	-0.020(15)	0.028(15)	0.0	-0.049(17)	0.170(14)	0.313(15)	0.301(11)	0.145(12)
$P_{3,+3}$	0.310(12)	0.293(12)	0.301(13)	0.288(13)	0.334(14)	-0.222(14)	-0.082(13)	0.081(12)	0.122(13)
$P_{3,-3}$	0.0	0.0	-0.124(18)	0.039(16)	-0.045(18)	0.059(13)	-0.048(14)	-0.027(13)	-0.111(14)

Multipoles	C10	C11	C12	C13	C14	C15	C16	C17	C18
$P_{1,+1}$	0.085(16)	-0.108(13)	-0.069(12)	0.0	0.128(13)	0.097(16)	0.109(12)	-0.028(10)	0.138(11)
$P_{1,-1}$	-0.142(14)	0.109(13)	-0.056(13)	-0.084(13)	-0.069(11)	0.0	-0.171(13)	0.0	0.0
$P_{1,0}$	0.026(12)	0.044(11)	0.129(12)	-0.123(12)	-0.123(12)	0.090(11)	-0.101(11)	-0.148(13)	-0.150(12)
$P_{2,0}$	-0.168(10)	0.0	-0.019(10)	-0.031(10)	-0.012(9)	-0.086(10)	0.0	0.046(9)	-0.024(10)
$P_{2,+1}$	0.0	-0.023(8)	0.0	0.046(9)	0.032(9)	-0.019(9)	-0.027(9)	0.018(9)	0.027(9)
$P_{2,-1}$	0.073(10)	-0.035(9)	0.010(8)	-0.018(9)	-0.010(9)	-0.031(9)	0.026(10)	0.055(9)	0.045(9)
$P_{2,+2}$	-0.042(11)	-0.027(9)	0.025(9)	-0.018(9)	-0.064(9)	0.086(8)	0.039(10)	-0.024(8)	-0.047(8)
$P_{2,-2}$	-0.050(10)	-0.041(8)	0.035(8)	-0.014(9)	0.034(9)	-0.016(9)	0.019(9)	-0.021(8)	0.041(9)
$P_{3,0}$	-0.058(18)	0.046(15)	0.055(15)	0.062(15)	0.021(15)	0.0	0.023(13)	-0.038(15)	0.029(14)
$P_{3,+1}$	-0.028(13)	-0.110(13)	-0.171(14)	0.0	-0.018(11)	-0.143(12)	-0.071(13)	0.067(13)	0.058(15)
$P_{3,-1}$	-0.019(14)	0.024(14)	-0.037(14)	0.119(13)	0.103(13)	-0.032(13)	0.042(15)	0.054(15)	0.160(14)
$P_{3,+2}$	-0.098(16)	0.104(14)	-0.051(12)	-0.130(15)	-0.058(13)	0.0	-0.106(16)	0.050(14)	-0.086(14)
$P_{3,-2}$	-0.024(16)	0.280(13)	0.201(13)	0.335(12)	0.327(14)	0.273(14)	0.288(13)	0.283(13)	0.134(12)
$P_{3,+3}$	0.361(14)	-0.110(14)	-0.134(13)	0.051(13)	-0.034(13)	-0.206(15)	-0.082(15)	0.048(11)	0.215(12)
$P_{3,-3}$	0.045(18)	0.099(12)	0.015(13)	-0.117(14)	-0.027(13)	0.036(14)	-0.081(11)	-0.018(12)	-0.117(13)

Table 13. Multipole populations (e^-) of Carbon atoms of 17*a*-estradiol•½H_2O.

Atoms	$P_{1,0}$	$P_{2,0}$
H1O	0.155(14)	0.021(18)
H2O	0.290(15)	0.033(19)
H1	0.128(15)	0.023(19)
H2	0.186(14)	0.038(18)
H4	0.161(14)	0.041(17)
H6A	0.192(9)	0.026(11)
H6B	0.192(9)	0.026(11)
H7A	0.140(8)	0.041(10)
H7B	0.140(8)	0.041(10)
H8	0.139(11)	0.0
H9	0.107(11)	0.015(15)
H11A	0.135(8)	0.057(12)
H11B	0.135(8)	0.057(12)
H12A	0.159(8)	0.043(10)
H12B	0.159(8)	0.043(10)
H14	0.107(13)	0.038(17)
H15A	0.165(9)	0.0
H15B	0.165(9)	0.0
H16A	0.183(9)	0.031(11)
H16B	0.183(9)	0.031(11)
H17	0.193(13)	0.0
H18A	0.134(7)	-0.018(9)
H18B	0.134(7)	-0.018(9)
H18C	0.134(7)	-0.018(9)
H3O	0.141(16)	0.035(23)

Table 14. Multipole populations (e^-) of Hydrogen atoms of 17*a*-estradiol•½H_2O.

Bond	$\rho(r_c)$	$\nabla^2\rho(r_c)$	R_{ij}	d_1	d_2	λ_1	λ_2	λ_3	ε
O1 – C3	2.120	-15.427	1.3757	0.8070	0.5687	-17.48	-15.51	17.57	0.13
O1 – H1O	2.170	-24.028	0.9703	0.7454	0.2249	-33.19	-32.56	41.72	0.02
O2 – C17	1.727	-5.757	1.4367	0.8340	0.6027	-11.99	-11.06	17.30	0.08
O2 – H2O	2.370	-37.913	0.9701	0.7433	0.2267	-37.48	-36.47	36.04	0.03
C1 – C2	2.237	-21.462	1.3953	0.6846	0.7107	-16.78	-14.23	9.54	0.18
C1 – C10	2.179	-20.448	1.4025	0.7211	0.6814	-16.21	-13.30	9.06	0.22
C1 – H1	1.993	-17.855	1.0801	0.6682	0.4119	-18.44	-17.63	18.22	0.05
C2 – C3	2.127	-19.668	1.3965	0.6541	0.7424	-16.14	-13.30	9.77	0.21
C2 – H2	2.059	-19.553	1.0801	0.6492	0.4309	-18.84	-17.27	16.56	0.09
C3 – C4	2.195	-20.099	1.3957	0.6645	0.7313	-17.10	-13.55	10.55	0.26
C4 – C5	2.158	-19.740	1.4048	0.7200	0.6848	-15.80	-13.25	9.31	0.19
C4 – H4	1.797	-16.893	1.0805	0.6243	0.4562	-16.36	-14.58	14.04	0.12
C5 – C6	1.679	-11.363	1.5163	0.7319	0.7844	-11.53	-10.13	10.30	0.14
C5 – C10	2.165	-21.077	1.4113	0.7604	0.6510	-16.47	-13.10	8.49	0.26
C6 – C7	1.728	-10.606	1.5301	0.7886	0.7415	-11.40	-10.59	11.38	0.08
C6 – H6A	1.791	-13.393	1.0901	0.6155	0.4747	-15.37	-12.82	14.79	0.20
C6 – H6B	1.812	-13.339	1.0906	0.6185	0.4721	-15.23	-13.08	14.97	0.16
C7 – C8	1.692	-11.578	1.5280	0.8049	0.7231	-11.55	-10.52	10.49	0.10
C7 – H7A	1.949	-17.580	1.0902	0.6472	0.4431	-17.72	-16.49	16.63	0.07
C7 – H7B	1.778	-14.845	1.0901	0.6271	0.4631	-14.99	-14.84	14.99	0.01
C8 – C9	1.630	-9.845	1.5468	0.8050	0.7419	-10.55	-10.01	10.72	0.05
C8 – C14	1.667	-11.245	1.5278	0.7631	0.7647	-11.17	-10.58	10.50	0.06
C8 – H8	1.880	-14.232	1.1000	0.6681	0.4319	-16.32	-15.97	18.06	0.02
C9 – C10	1.700	-10.657	1.5255	0.7407	0.7848	-11.32	-9.98	10.65	0.13
C9 – C11	1.645	-10.410	1.5394	0.7939	0.7456	-10.79	-10.30	10.68	0.05
C9 – H9	1.825	-14.327	1.1002	0.6682	0.4320	-16.31	-15.61	17.60	0.04

Table 15. Topological properties of bond critical points in 17*a*-estradiol•½H_2O.

Bond	$\rho(r_c)$	$\nabla^2\rho(r_c)$	R_{ij}	d_1	d_2	λ_1	λ_2	λ_3	ε
C11 – C12	1.550	-8.036	1.5406	0.7751	0.7655	-9.84	-9.04	10.84	0.09
C11 – H11A	2.023	-18.370	1.0906	0.6579	0.4326	-18.66	-17.46	17.74	0.07
C11 – H11B	1.965	-16.884	1.0901	0.6517	0.4383	-17.38	-16.77	17.27	0.04
C12 – C13	1.717	-10.751	1.5339	0.7449	0.7889	-10.95	-10.88	11.08	0.01
C12 – H12A	1.890	-16.414	1.0902	0.6346	0.4556	-16.38	-15.72	15.69	0.04
C12 – H12B	2.031	-17.189	1.0903	0.6553	0.4350	-17.75	-17.29	17.85	0.03
C13 – C14	1.632	-9.730	1.5434	0.7366	0.8068	-10.29	-10.06	10.61	0.02
C13 – C17	1.647	-8.917	1.5507	0.7879	0.7628	-11.22	-9.62	11.93	0.17
C13 – C18	1.688	-10.826	1.5436	0.7674	0.7762	-11.27	-10.57	11.02	0.07
C14 – C15	1.647	-9.329	1.5399	0.7335	0.8064	-10.51	-9.95	11.14	0.06
C14 – H14	1.825	-14.820	1.1001	0.6597	0.4403	-16.15	-15.66	16.99	0.03
C15 – C16	1.592	-9.009	1.5578	0.8083	0.7495	-10.37	-9.69	11.05	0.07
C15 – H15A	1.830	-15.696	1.0910	0.6296	0.4613	-16.67	-14.53	15.51	0.15
C15 – H15B	1.918	-15.537	1.0908	0.6429	0.4478	-17.05	-15.35	16.86	0.11
C16 – C17	1.695	-10.605	1.5467	0.8271	0.7196	-11.51	-10.72	11.63	0.07
C16 – H16A	1.889	-16.413()	1.0901	0.6256	0.4644	-16.48	-14.99	15.05	0.10
C16 – H16B	1.918	-15.979()	1.0906	0.6336	0.4570	-16.06	-15.91	15.98	0.01
C17 – H17	1.975	-15.631	1.1004	0.6469	0.4535	-17.73	-16.64	18.74	0.07
C18 – H18A	2.060	-16.196	1.0601	0.6334	0.4267	-18.22	-16.43	18.45	0.11
C18 – H18B	1.851	-13.606	1.0638	0.6195	0.4443	-16.56	-14.36	17.31	0.15
C18 – H18C	1.910	-13.904	1.0605	0.6196	0.4408	-17.12	-14.02	17.24	0.22
O3 – H3O	2.413	-67.609	0.9607	0.7967	0.1640	-51.40	-48.06	31.85	0.07

Table 16. Topological properties of bond critical points in 17*a*-estradiol•½H_2O continued.

Bond	$\rho(r_c)$	$\nabla^2\rho(r_c)$	R_{ij}	d_1	d_2	λ_1	λ_2	λ_3	ε
O1–H1O··O3	0.124	3.237	1.8746	1.2378	0.6367	-0.75	-0.68	4.67	0.11
O2–H2O··O1	0.094	2.431	2.0909	0.7521	1.3388	-0.70	-0.47	3.60	0.49
O3–H3O··O2	0.165	2.371	1.9303	0.6247	1.3056	-0.99	-0.92	4.28	0.08

Table 17. Topological properties of bond critical points in the hydrogen bonds of 17*a*-estradiol•½H_2O.

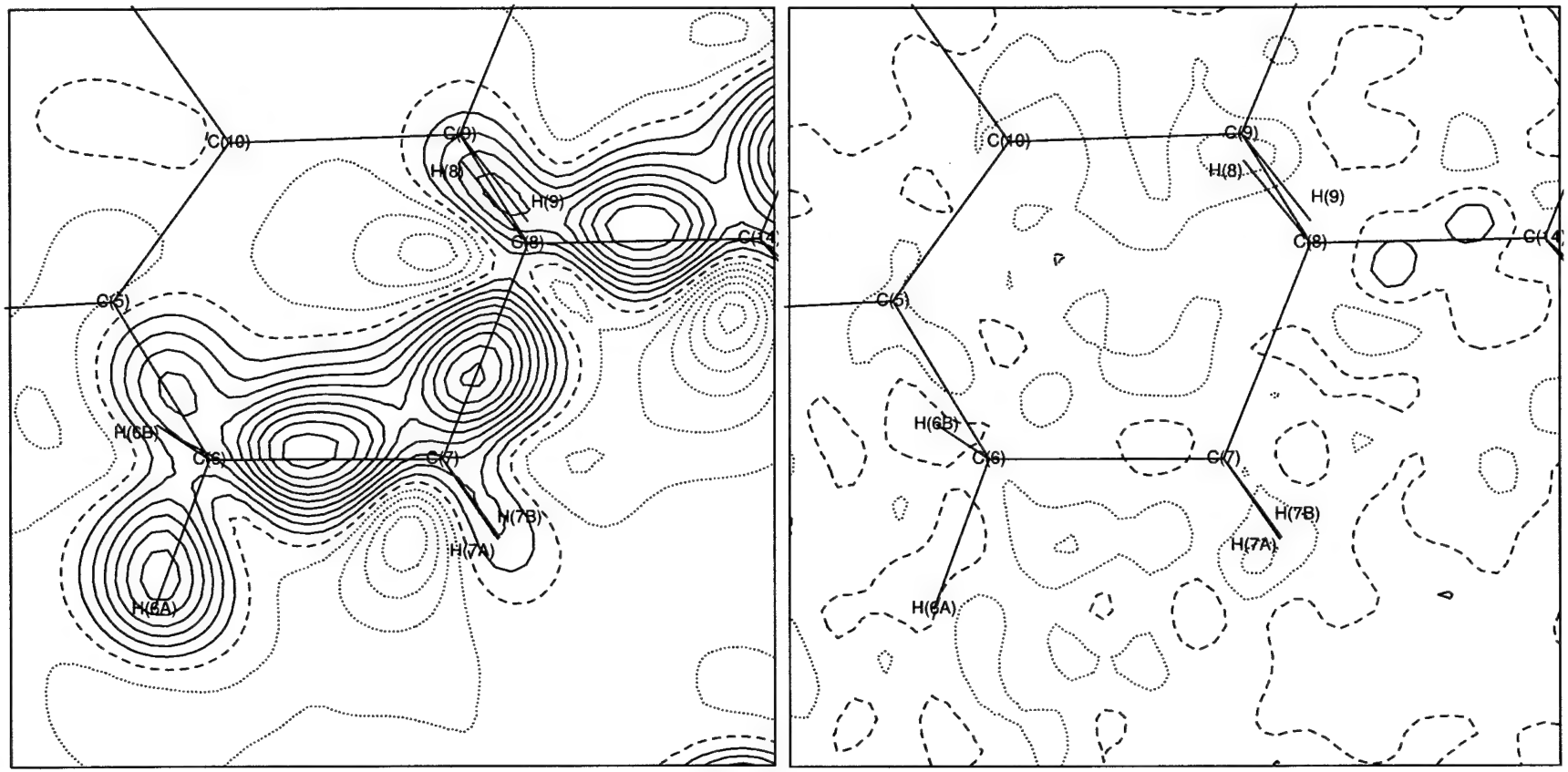

Figure 3. Dynamic model map and residual map in the C6 – C7 – C8 plane of 17*a*-estradiol•½H_2O. Contour intervals are 0.05 e$Å^{-3}$ with solid lines positive, dashed lines zero, and dotted lines negative.

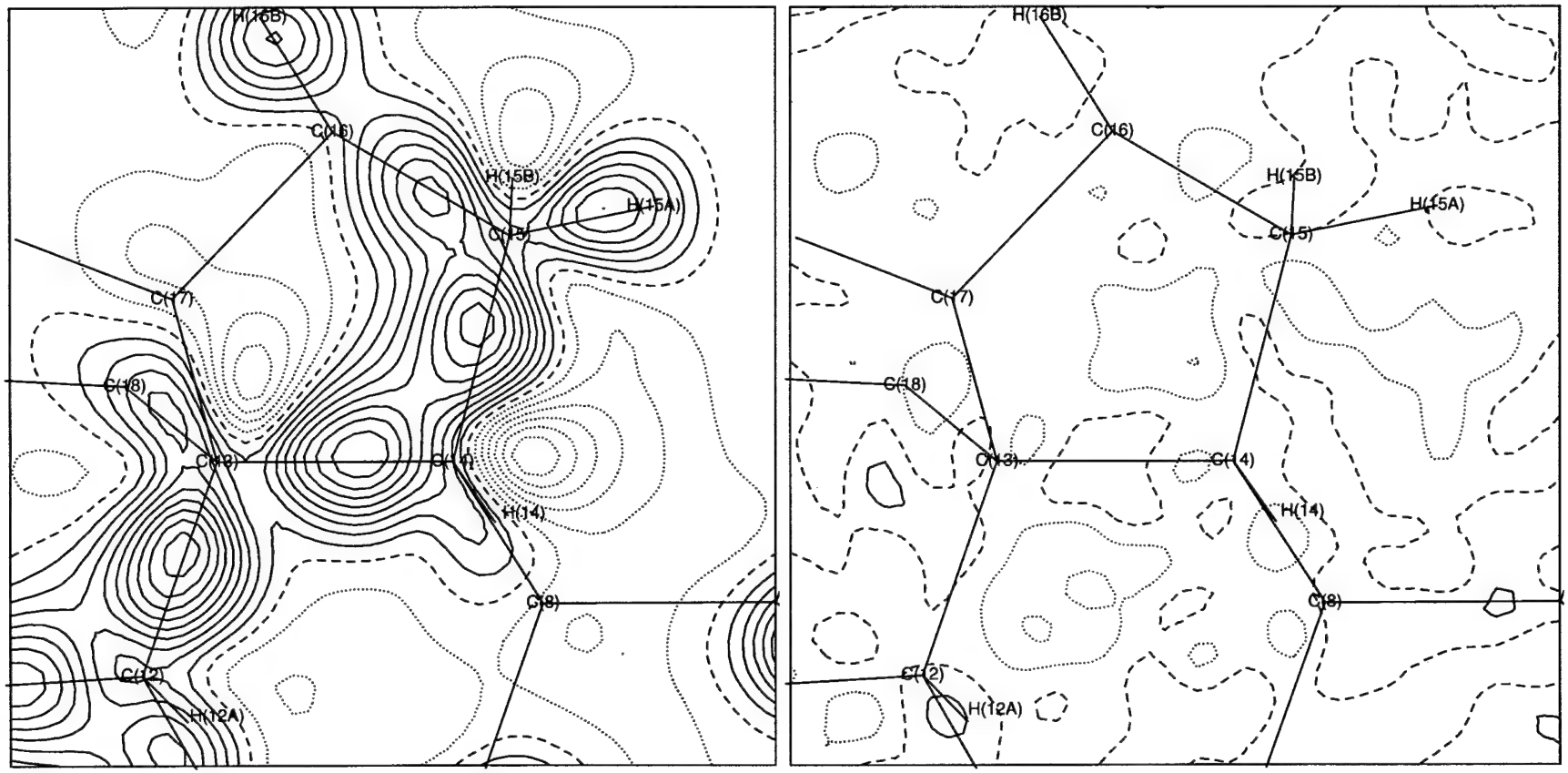

Figure 4. Dynamic model map and residual map in the C13 – C14 – C15 plane of 17*a*-estradiol•½H_2O. Contour intervals are 0.05 eÅ^{-3} with solid lines positive, dashed lines zero, and dotted lines negative.

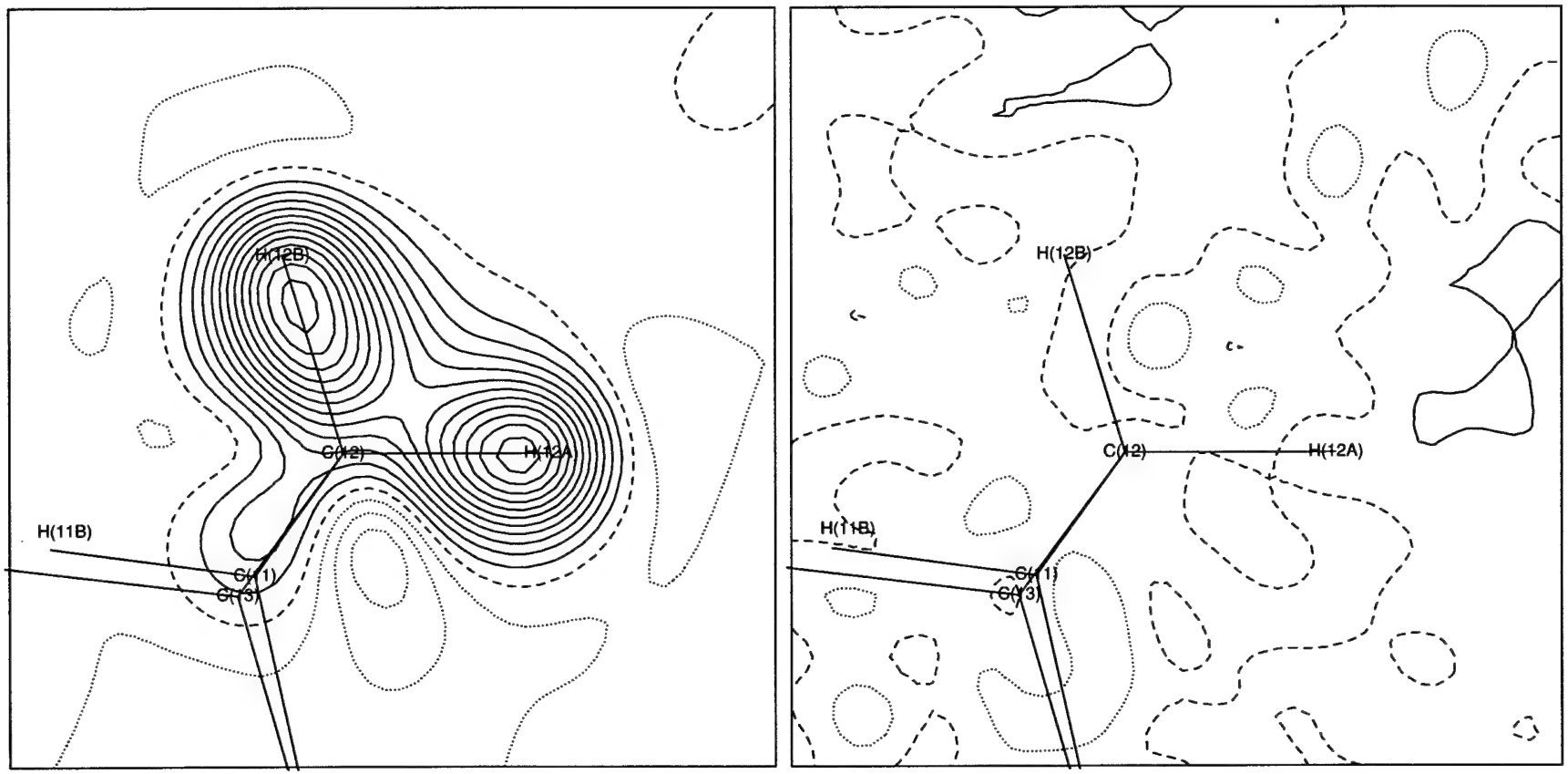

Figure 5. Dynamic model map and residual map in the C12 – H12A – H12B plane of 17*a*-estradiol•½H_2O. Contour intervals are 0.05 e$Å^{-3}$ with solid lines positive, dashed lines zero, and dotted lines negative.

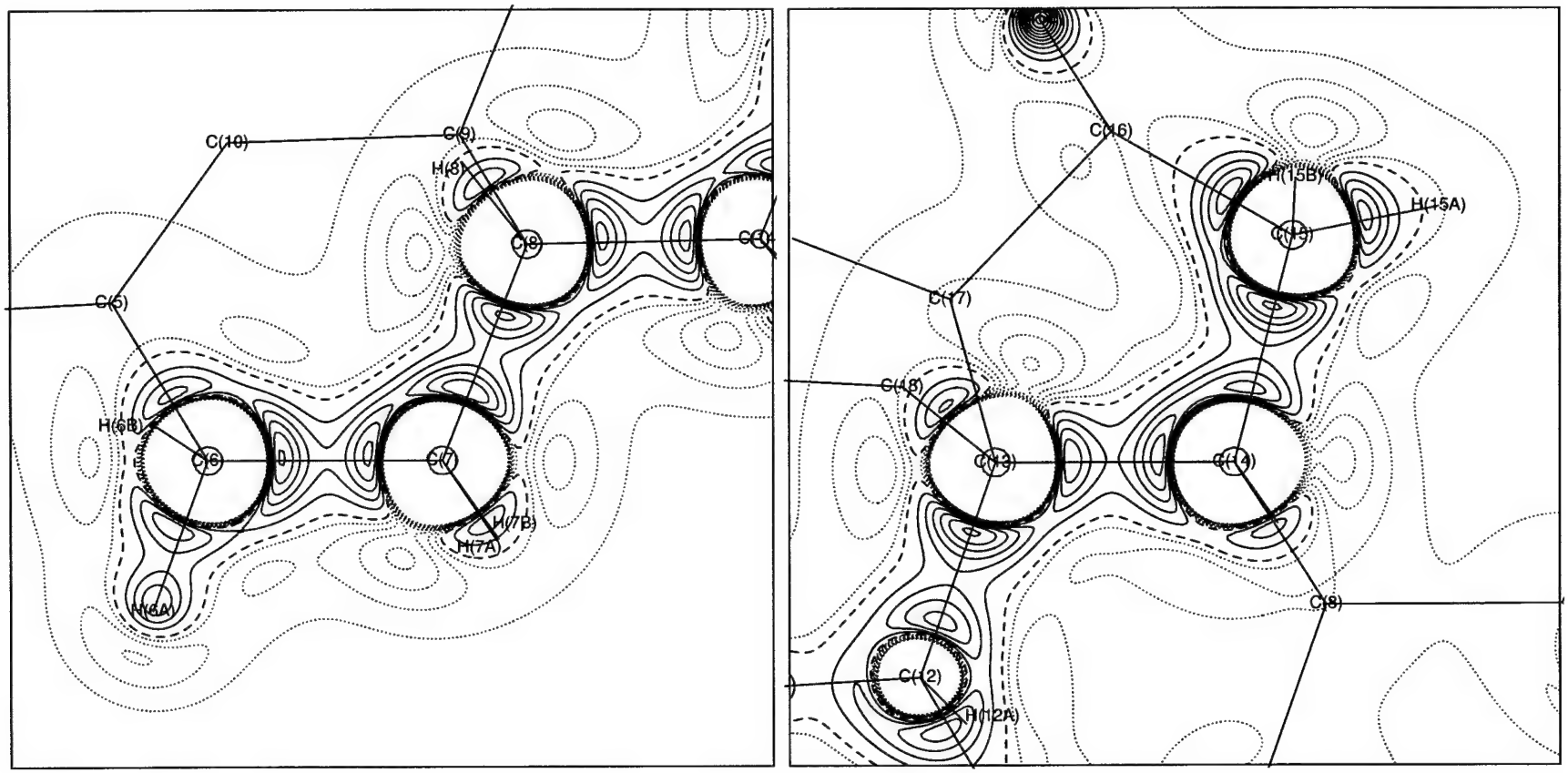

Figure 6. The Laplacian of the total electron density of atoms at rest in the C6 – C7 – C8 and C13 – C14 – C15 planes of 17*a*-estradiol•½H_2O. Contour intervals are 5 e$Å^{-5}$ starting at 5 e$Å^{-5}$ (solid blue lines), -2 e$Å^{-5}$ starting at -2 e$Å^{-5}$ (dotted red lines), and the dashed line equals 0 e$Å^{-5}$.

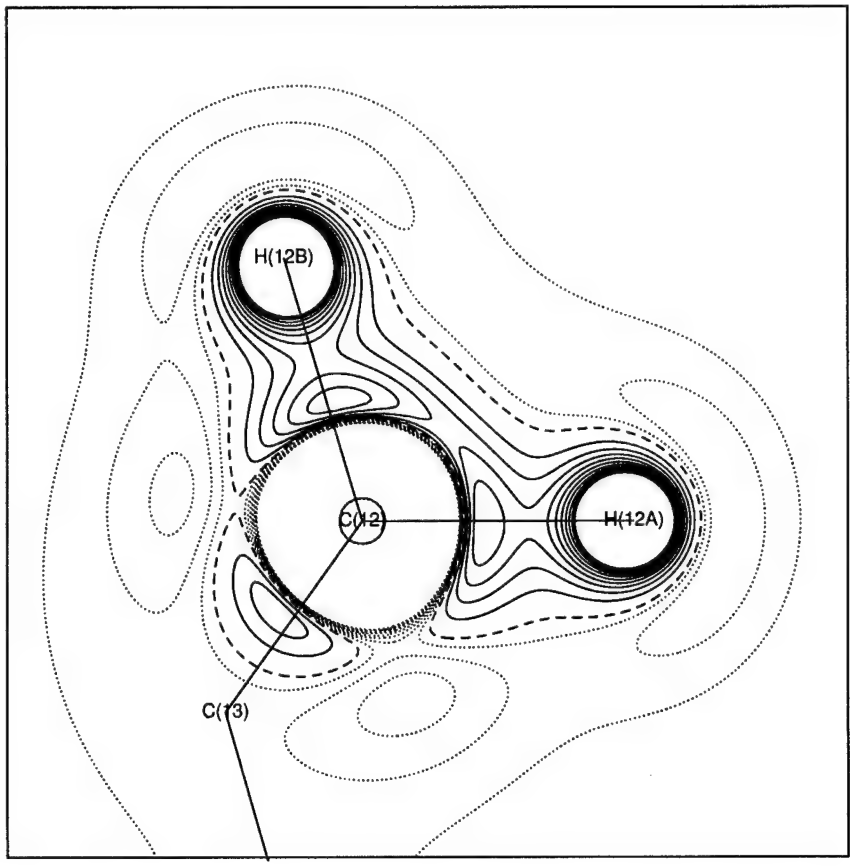

Figure 7. The Laplacian of the total electron density of atoms at rest in the H12A – C12 – H12B plane of 17*a*-estradiol•½H_2O. Contour intervals are 5 eÅ^{-5} starting at 5 eÅ^{-5} (solid blue lines), -2 eÅ^{-5} starting at -2 eÅ^{-5} (dotted red lines), and the dashed line plots 0 eÅ^{-5}.

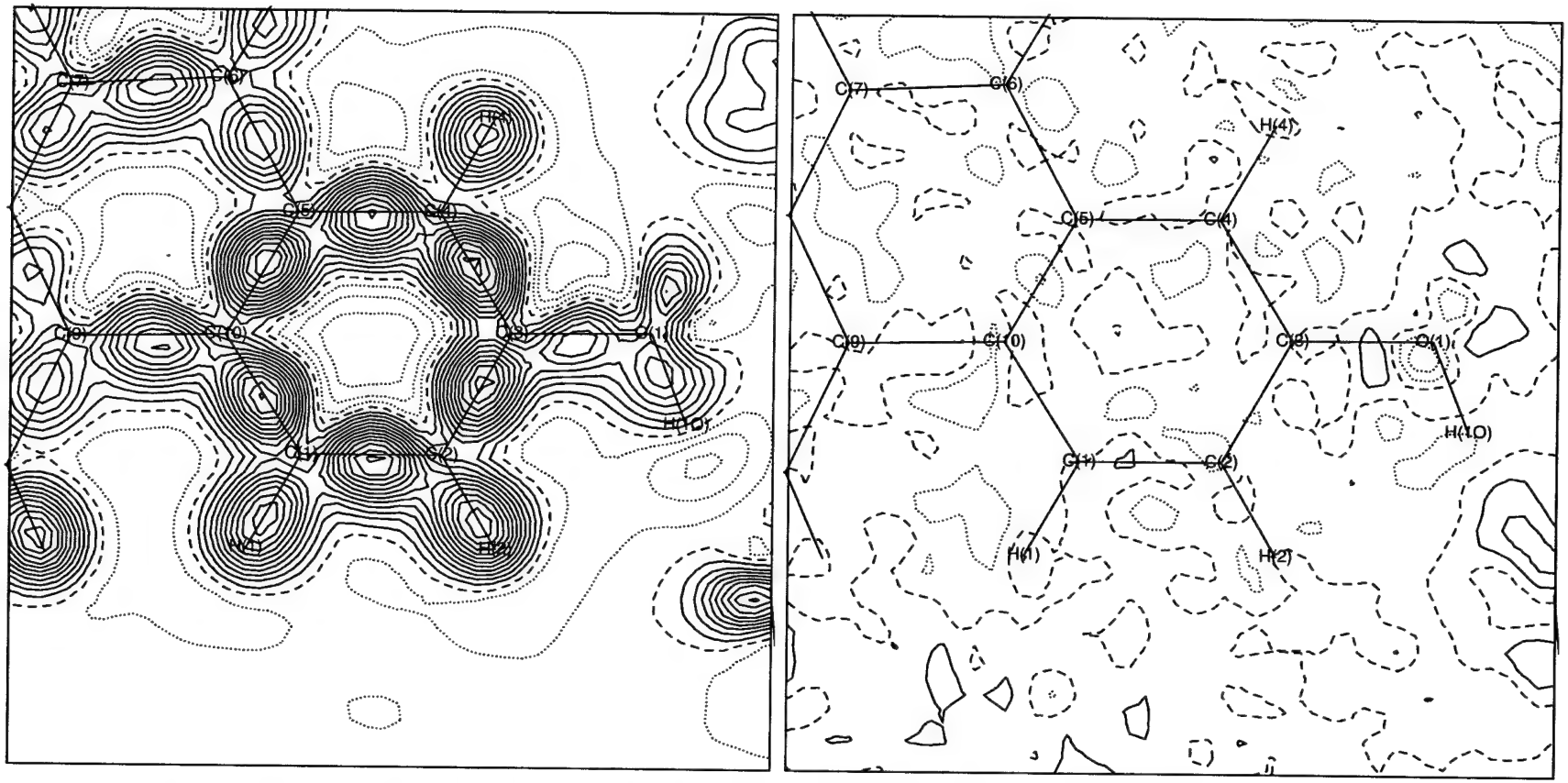

Figure 8. Dynamic model map and residual map in the plane of the aromatic ring of 17*a*-estradiol•½H_2O. Contour intervals are 0.05 e$Å^{-3}$ with solid lines positive, dashed lines zero, and dotted lines negative.

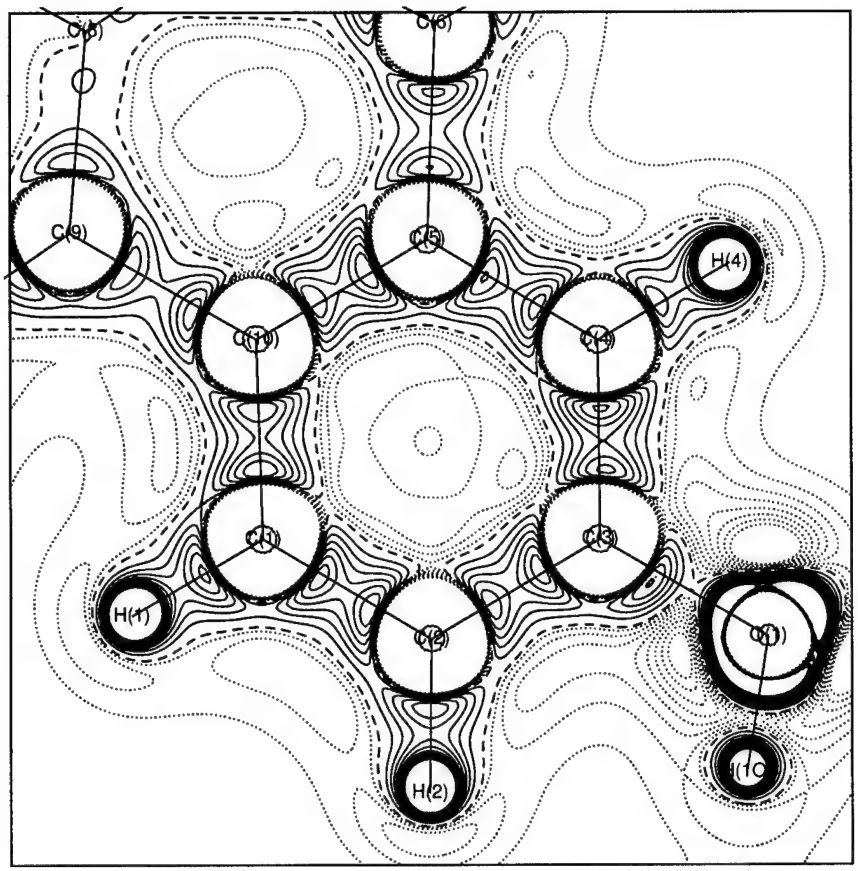

Figure 9. The Laplacian of the total electron density of atoms at rest in the plane of the aromatic ring of 17*a*-estradiol•½H_2O. Contour intervals are 5 eÅ^{-5} starting at 5 eÅ^{-5} (solid blue lines), -2 eÅ^{-5} starting at -2 eÅ^{-5} (dotted red lines), and the dashed line plots 0 eÅ^{-5}.

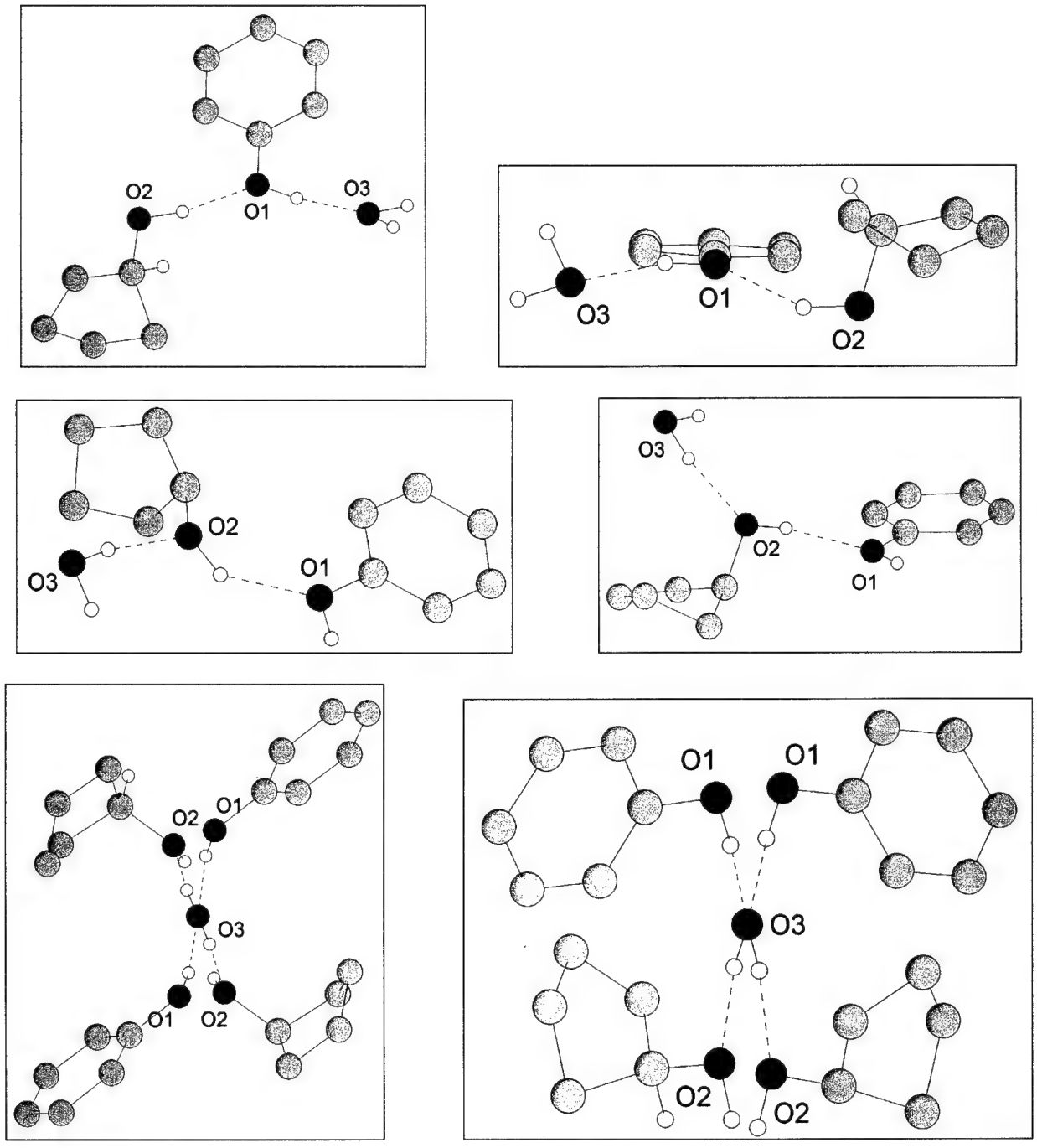

Figure 10. Geometry of hydrogen bonding interactions of 17*a*-estradiol•½H_2O.

Appendix E.

Charge density study of estrone

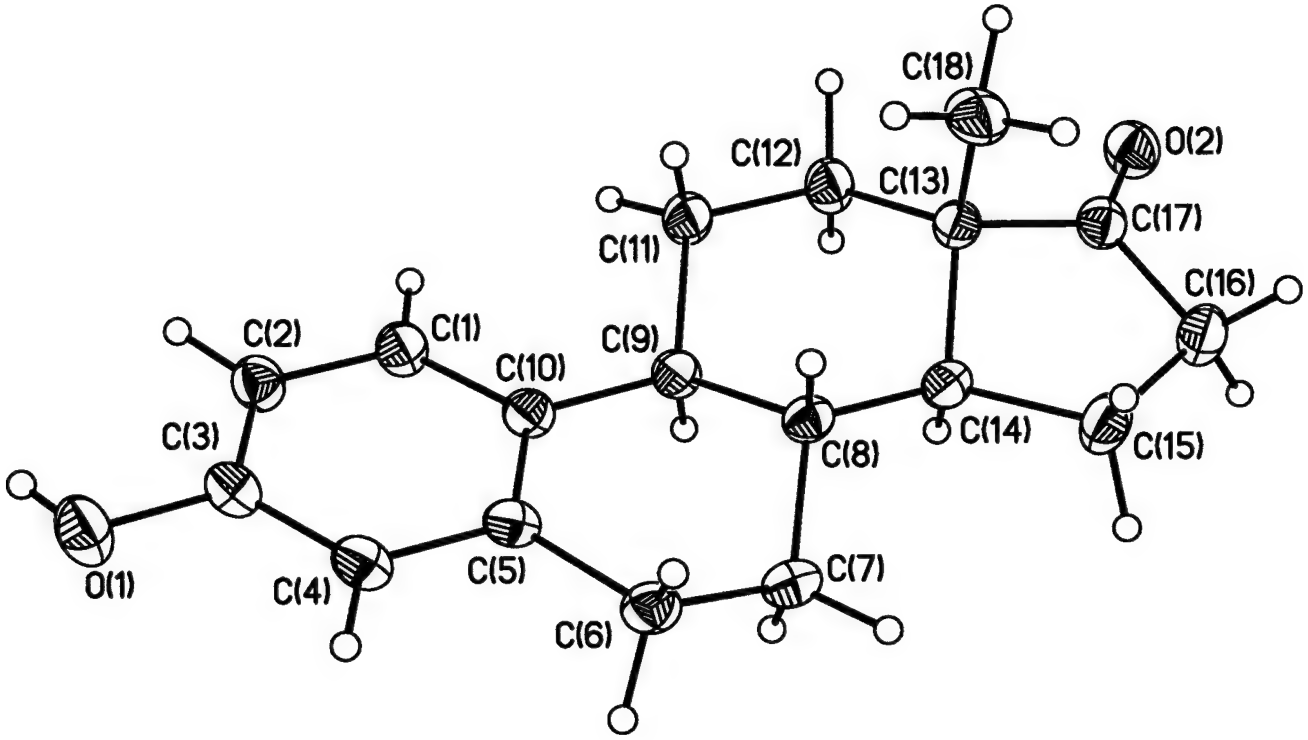

Figure 1a. The estrone molecule with 50% probability thermal ellipsoids for non-hydrogen atoms.

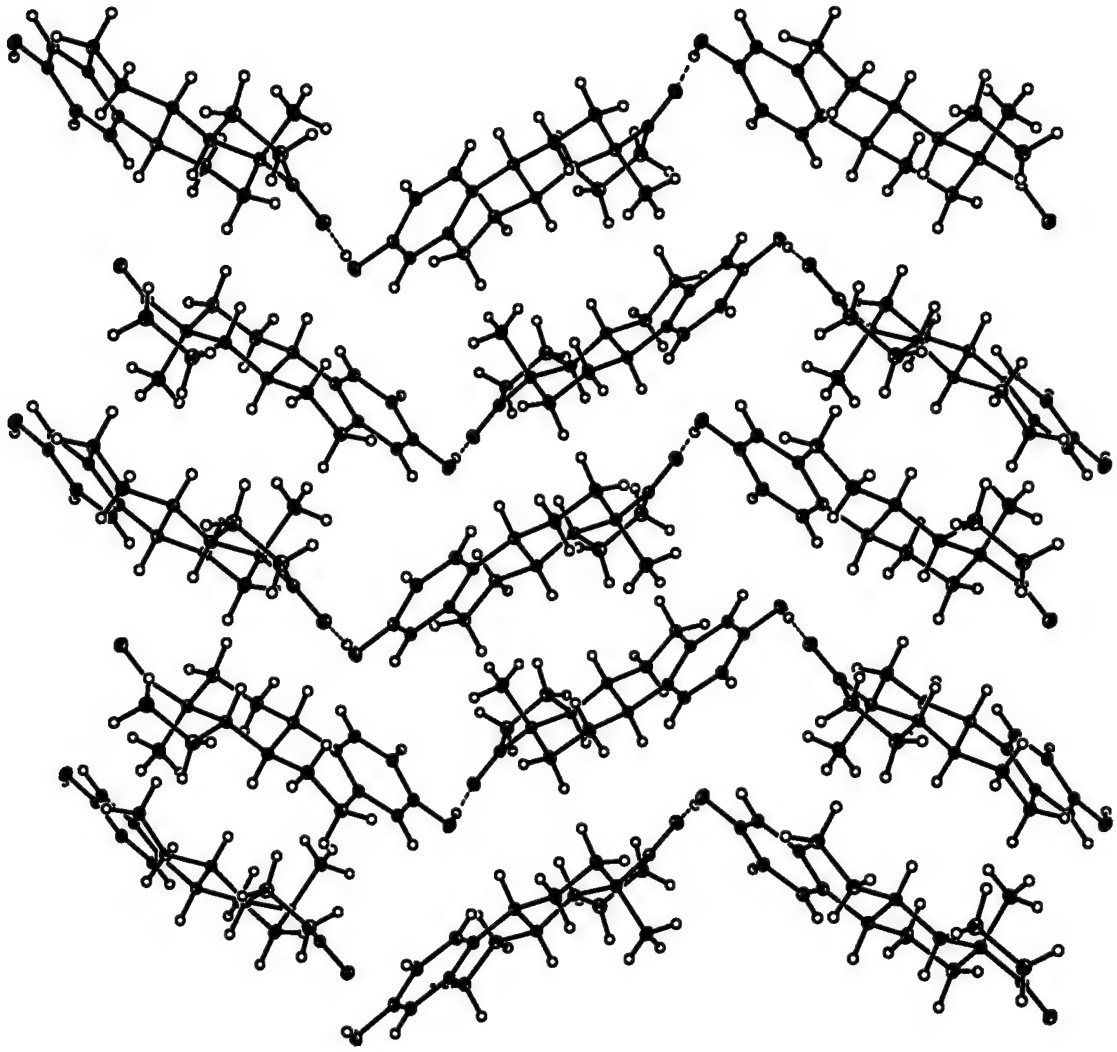

Figure 1b. Packing diagram showing the hydrogen bonds.

Experimental

Compound name:	estrone
Chemical formula:	$C_{18}H_{22}O_2$
Chemical formula weight:	270.36
Crystal density:	1.263
Crystal size, mm	0.2×0.25×0.30
μ, mm^{-1}	0.05
Unit cell parameters:	
a (Å)	7.7618(1)
b (Å)	9.9536(1)
c (Å)	18.4055(1)
V (Å)	1421.97(2)
Z	4
F(000)	584
Space group	$P2_12_12_1$
Temperature:	92.0(2)
Radiation(Å):	Ag K_α (λ=0.56086 Å)
h_{min}/h_{max}	-20/20
k_{min}/k_{max}	-26/25
l_{min}/l_{max}	-48/48
$\theta_{min}/\theta_{max}$	1.75/48.26
Intensity decay	0 %
Total No. of reflections	90695
No. of independent reflections	16278
R_{int}	0.0231
No. of reflections used	8875
Criterion	$I>3\sigma$
Refinement on	F^2
Total No. of parameters	810
Weighting scheme	$w=1/\sigma^2$
Multipole refinement:	
$R(F^2)$	0.0279
$R_w(F^2)$	0.0366
S	1.3337
κ- refinement:	
R	0.0445
R_w	0.0611
S	1.54

Atomic coordinates and U_{iso} in estrone

Atom	x	y	x	U_{iso}
O(1)	-1.34702(4)	-0.80621(3)	-0.31144(2)	0.022
O(2)	-0.81887(4)	-0.28634(3)	0.15628(2)	0.021
C(1)	-1.27691(5)	-0.55423(4)	-0.16813(2)	0.017
C(2)	-1.35941(5)	-0.62550(4)	-0.22323(2)	0.018
C(3)	-1.27233(5)	-0.73037(4)	-0.25798(2)	0.017
C(4)	-1.10329(5)	-0.76064(4)	-0.23767(2)	0.017
C(5)	-1.02040(5)	-0.68873(4)	-0.18217(2)	0.015
C(6)	-0.83709(5)	-0.72801(4)	-0.16266(2)	0.017
C(7)	-0.74637(5)	-0.62131(4)	-0.11661(2)	0.017
C(8)	-0.86413(4)	-0.57930(3)	-0.05415(2)	0.014
C(9)	-1.02082(5)	-0.50316(4)	-0.08568(2)	0.015
C(10)	-1.10798(5)	-0.58421(4)	-0.14580(2)	0.015
C(11)	-1.14594(5)	-0.45811(4)	-0.02538(2)	0.019
C(12)	-1.05678(5)	-0.37607(4)	0.03510(2)	0.019
C(13)	-0.90195(5)	-0.45307(4)	0.06482(2)	0.015
C(14)	-0.77799(5)	-0.48930(4)	0.00219(2)	0.015
C(15)	-0.61274(5)	-0.53505(4)	0.04134(2)	0.020
C(16)	-0.59941(5)	-0.43575(4)	0.10593(2)	0.021
C(17)	-0.78054(5)	-0.37816(4)	0.11509(2)	0.017
C(18)	-0.96009(6)	-0.57650(4)	0.10964(2)	0.022
H(1A)	-1.4610(9)	-0.7709(7)	-0.3207(3)	0.038(2)
H(1)	-1.3493(8)	-0.4749(6)	-0.1419(3)	0.049(2)
H(2)	-1.4904(9)	-0.6010(7)	-0.2387(3)	0.045(2)
H(4)	-1.0358(9)	-0.8413(7)	-0.2651(4)	0.052(2)
H(6A)	-0.8420(9)	-0.8227(6)	-0.1328(3)	0.054(2)
H(6B)	-0.7634(8)	-0.7498(7)	-0.2118(3)	0.052(2)
H(7A)	-0.6238(8)	-0.6610(6)	-0.0970(3)	0.057(2)
H(7B)	-0.7152(8)	-0.5326(6)	-0.1490(3)	0.049(2)
H(8)	-0.9113(8)	-0.6713(7)	-0.0278(3)	0.052(2)
H(9)	-0.9648(8)	-0.4117(6)	-0.1094(3)	0.052(2)
H(11A)	-1.2105(8)	-0.5456(7)	-0.0021(3)	0.043(2)
H(11B)	-1.2491(9)	-0.3978(7)	-0.0491(4)	0.054(2)
H(12A)	-1.1501(8)	-0.3501(6)	0.0772(3)	0.049(2)
H(12B)	-1.0124(8)	-0.2810(6)	0.0121(3)	0.047(2)
H(14)	-0.7469(7)	-0.3938(7)	-0.0248(3)	0.048(2)
H(15A)	-0.6236(9)	-0.6387(7)	0.0602(3)	0.051(2)
H(15B)	-0.5003(10)	-0.5324(7)	0.0057(4)	0.056(2)
H(16A)	-0.5572(9)	-0.4816(7)	0.1568(3)	0.052(2)
H(16B)	-0.5107(9)	-0.3521(7)	0.0974(4)	0.063(2)
H(18A)	-1.0328(8)	-0.6461(6)	0.0787(3)	0.057(2)
H(18B)	-1.0397(8)	-0.5423(7)	0.1525(3)	0.058(2)
H(18C)	-0.8571(9)	-0.6322(7)	0.1324(3)	0.065(2)

U_{ij} values

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O(1)	0.0251(1)	0.0223(1)	0.0180(1)	0.0028(1)	-0.0043(1)	-0.0046(1)
O(2)	0.0215(1)	0.0207(1)	0.0200(1)	-0.0004(1)	-0.0016(1)	-0.0030(1)
C(1)	0.0162(1)	0.0177(1)	0.0170(1)	0.0038(1)	-0.0016(1)	-0.0022(1)
C(2)	0.0175(2)	0.0190(1)	0.0164(1)	0.0031(1)	-0.0018(1)	-0.0018(1)
C(3)	0.0194(2)	0.0174(1)	0.0132(1)	0.0020(1)	-0.0008(1)	-0.0007(1)
C(4)	0.0192(2)	0.0177(1)	0.0142(1)	0.0034(1)	0.0007(1)	-0.0009(1)
C(5)	0.0156(1)	0.0164(1)	0.0137(1)	0.0024(1)	0.0014(1)	0.0004(1)
C(6)	0.0157(2)	0.0181(1)	0.0176(1)	0.0035(1)	0.0020(1)	-0.0009(1)
C(7)	0.0140(1)	0.0175(1)	0.0198(1)	0.0014(1)	0.0032(1)	0.0004(1)
C(8)	0.0130(1)	0.0143(1)	0.0152(1)	0.0011(1)	0.0011(1)	0.0013(1)
C(9)	0.0146(1)	0.0153(1)	0.0144(1)	0.0028(1)	0.0001(1)	-0.0002(1)
C(10)	0.0150(1)	0.0153(1)	0.0146(1)	0.0031(1)	0.0002(1)	-0.0003(1)
C(11)	0.0140(1)	0.0254(2)	0.0171(1)	0.0049(1)	-0.0015(1)	-0.0043(1)
C(12)	0.0175(2)	0.0228(2)	0.0177(2)	0.0061(1)	-0.0021(1)	-0.0045(1)
C(13)	0.0140(1)	0.0160(1)	0.0147(1)	0.0000(1)	-0.0003(1)	0.0016(1)
C(14)	0.0129(1)	0.0154(1)	0.0163(1)	0.0000(1)	0.0003(1)	0.0015(1)
C(15)	0.0146(2)	0.0231(2)	0.0237(2)	0.0031(1)	-0.0030(1)	-0.0022(1)
C(16)	0.0158(2)	0.0238(2)	0.0224(2)	0.0000(1)	-0.0040(1)	-0.0015(1)
C(17)	0.0163(1)	0.0174(1)	0.0166(1)	-0.0013(1)	-0.0011(1)	0.0016(1)
C(18)	0.0243(2)	0.0222(2)	0.0182(2)	-0.0070(1)	0.0012(1)	0.0037(1)

Bond lengths

O(1)	C(3)	1.3691(4)
O(1)	H(1A)	0.967(7)
O(2)	C(17)	1.2242(5)
C(1)	C(2)	1.3934(5)
C(1)	C(10)	1.4062(5)
C(1)	H(1)	1.083(6)
C(2)	C(3)	1.3984(5)
C(2)	H(2)	1.083(7)
C(3)	C(4)	1.3971(5)
C(4)	C(5)	1.4035(5)
C(4)	H(4)	1.083(7)
C(5)	C(6)	1.5186(5)
C(5)	C(10)	1.4115(5)
C(6)	C(7)	1.5304(5)
C(6)	H(6A)	1.092(6)
C(6)	H(6B)	1.092(6)
C(7)	C(8)	1.5270(5)
C(7)	H(7A)	1.092(6)
C(7)	H(7B)	1.092(6)
C(8)	C(14)	1.5247(5)
C(8)	H(8)	1.099(7)
C(9)	C(10)	1.5274(5)
C(9)	H(9)	1.099(6)
C(11)	H(11A)	1.092(7)
C(11)	H(11B)	1.092(7)
C(12)	C(13)	1.5268(5)
C(12)	H(12A)	1.092(6)
C(12)	H(12B)	1.092(6)
C(13)	C(17)	1.5165(5)
C(14)	H(14)	1.099(7)
C(15)	H(15A)	1.092(7)
C(15)	H(15B)	1.092(7)
C(16)	C(17)	1.5276(5)
C(16)	H(16A)	1.092(7)
C(16)	H(16B)	1.092(7)
C(18)	H(18A)	1.059(6)
C(18)	H(18B)	1.059(6)
C(18)	H(18C)	1.059(7)

Bond angles

C(3) - O(1) - H(1A)	108.3(5)
C(2) - C(1) - C(10)	122.2(1)
C(2) - C(1) - H(1)	117.2(4)
C(10) - C(1) - H(1)	120.5(4)
C(1) - C(2) - C(3)	119.4(1)
C(1) - C(2) - H(2)	120.5(4)
C(3) - C(2) - H(2)	120.1(4)
O(1) - C(3) - C(2)	122.4(1)
O(1) - C(3) - C(4)	118.1(1)
C(2) - C(3) - C(4)	119.5(1)
C(3) - C(4) - C(5)	121.0(1)
C(3) - C(4) - H(4)	119.3(4)
C(5) - C(4) - H(4)	119.7(4)
C(4) - C(5) - C(6)	118.1(1)
C(4) - C(5) - C(10)	120.0(1)
C(6) - C(5) - C(10)	121.9(1)
C(5) - C(6) - C(7)	112.5(1)
C(5) - C(6) - H(6A)	108.0(4)
C(5) - C(6) - H(6B)	110.2(4)
C(7) - C(6) - H(6A)	109.7(4)
C(7) - C(6) - H(6B)	110.8(4)
H(6A) - C(6) - H(6B)	105.3(5)
C(6) - C(7) - C(8)	109.4(1)
C(6) - C(7) - H(7A)	109.5(4)
C(6) - C(7) - H(7B)	111.2(4)
C(8) - C(7) - H(7A)	111.8(4)
C(8) - C(7) - H(7B)	108.8(4)
H(7A) - C(7) - H(7B)	106.3(5)
C(7) - C(8) - C(14)	114.2(1)
C(7) - C(8) - H(8)	107.7(4)
C(14) - C(8) - H(8)	109.6(4)
C(10) - C(9) - H(9)	108.9(4)
C(1) - C(10) - C(5)	117.8(1)
C(1) - C(10) - C(9)	120.8(1)
C(5) - C(10) - C(9)	121.3(1)
H(11A)- C(11) - H(11B)	105.0(5)
C(13) - C(12) - H(12A)	112.7(4)
C(13) - C(12) - H(12B)	109.0(4)
H(12A)- C(12) - H(12B)	106.2(5)
C(12) - C(13) - C(17)	117.4(1)
C(8) - C(14) - H(14)	107.3(3)
H(15A)- C(15) - H(15B)	106.0(6)
C(17) - C(16) - H(16A)	109.8(4)
C(17) - C(16) - H(16B)	108.1(4)
H(16A)- C(16) - H(16B)	104.6(5)
O(2) - C(17) - C(13)	126.4(1)
O(2) - C(17) - C(16)	124.9(1)
C(13) - C(17) - C(16)	108.7(1)
H(18A)- C(18) - H(18B)	107.5(5)
H(18A)- C(18) - H(18C)	105.8(5)
H(18B)- C(18) - H(18C)	108.3(5)

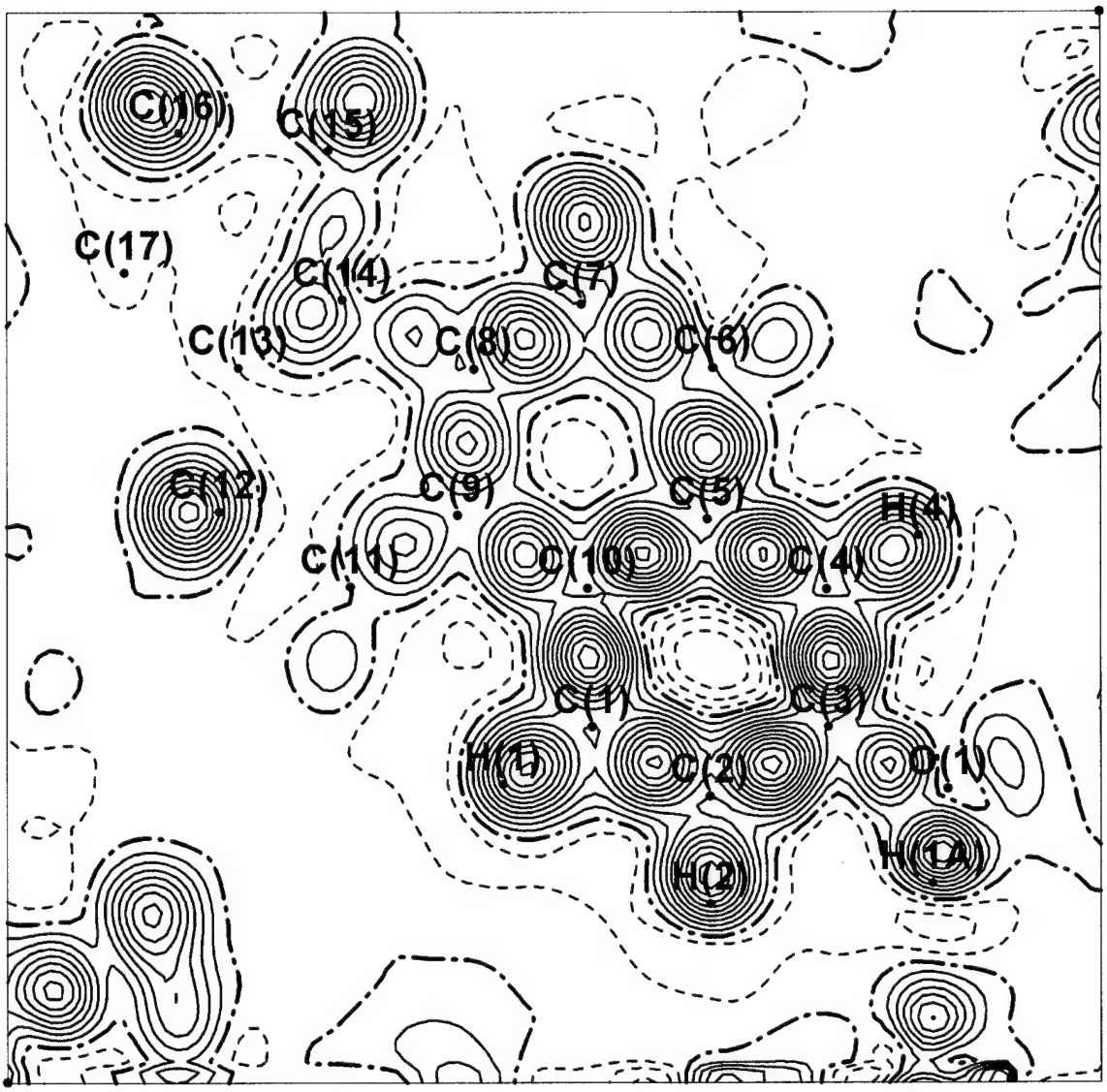

Figure 2a. Dynamic Fourier multipole map in the aromatic ring plane. Contour interval is 0.05 eÅ^{-3}.

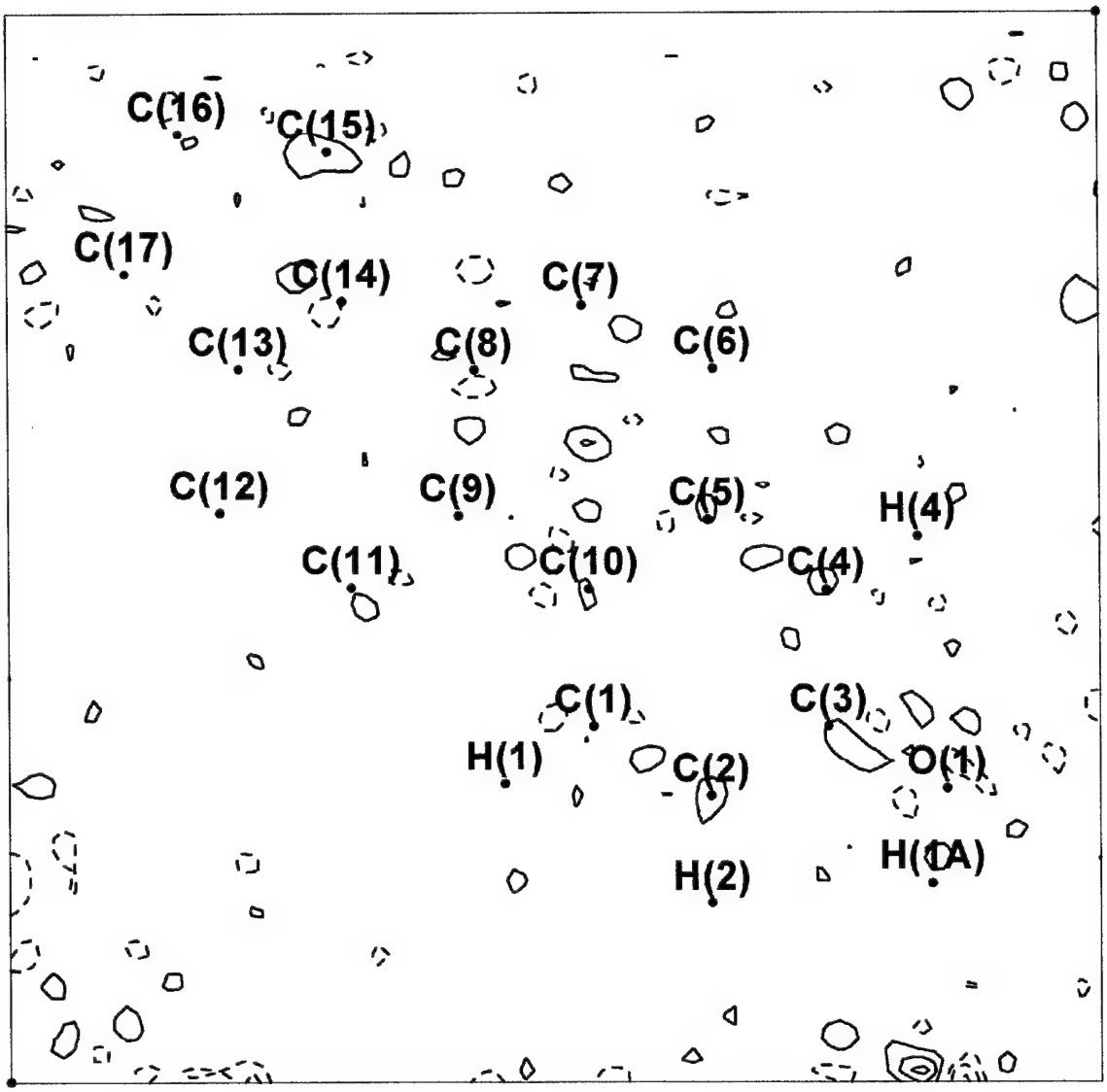

Figure 2b. Residual map in the aromatic ring plane.

Contour interval is 0.05 eÅ^{-3}.

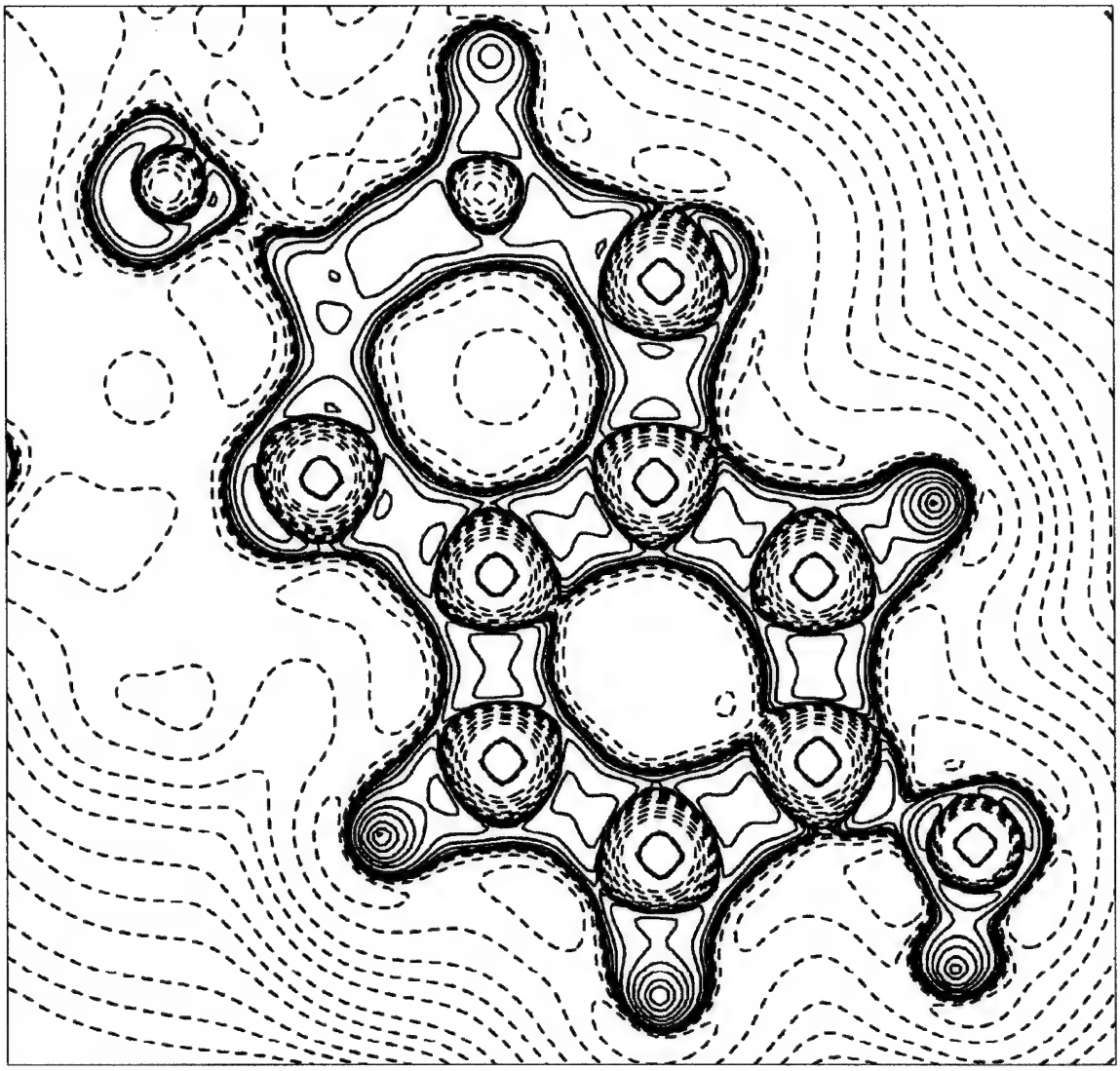

Figure 2c. The Laplacian of the electron density in the aromatic ring plane. Contour interval is 2,4,8 x 10^{-3-+3} eÅ^{-5}.

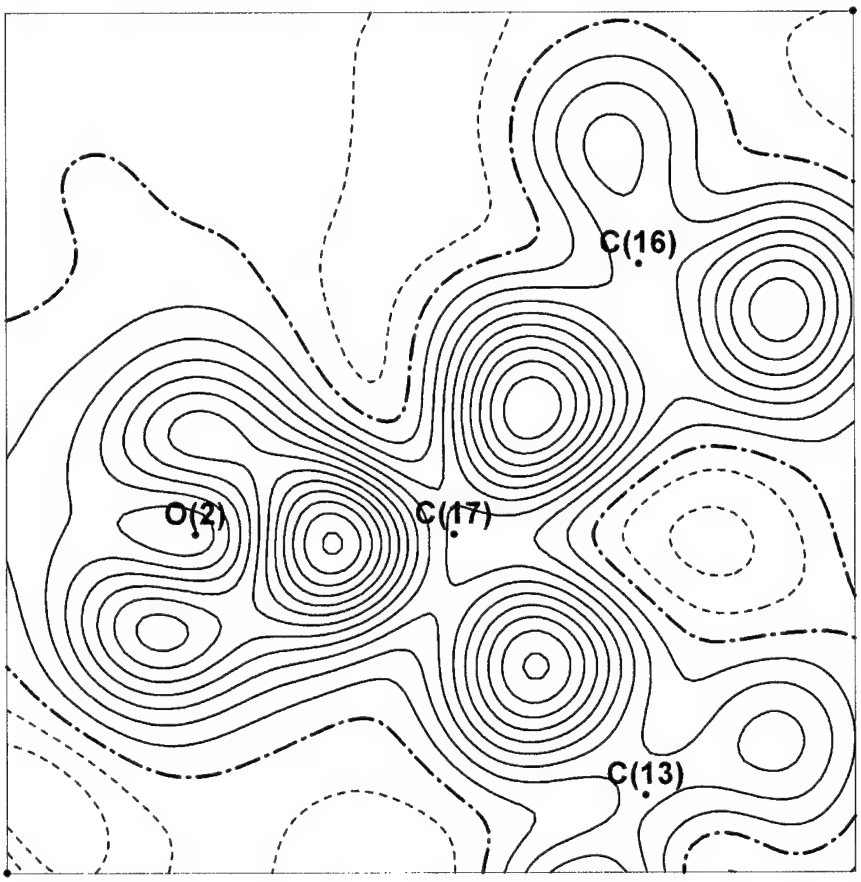

Figure 3a. Dynamic Fourier multipole electron density map in the O(2)-C(17)-C(16) plane. Contour interval is 0.05 $eÅ^{-3}$.

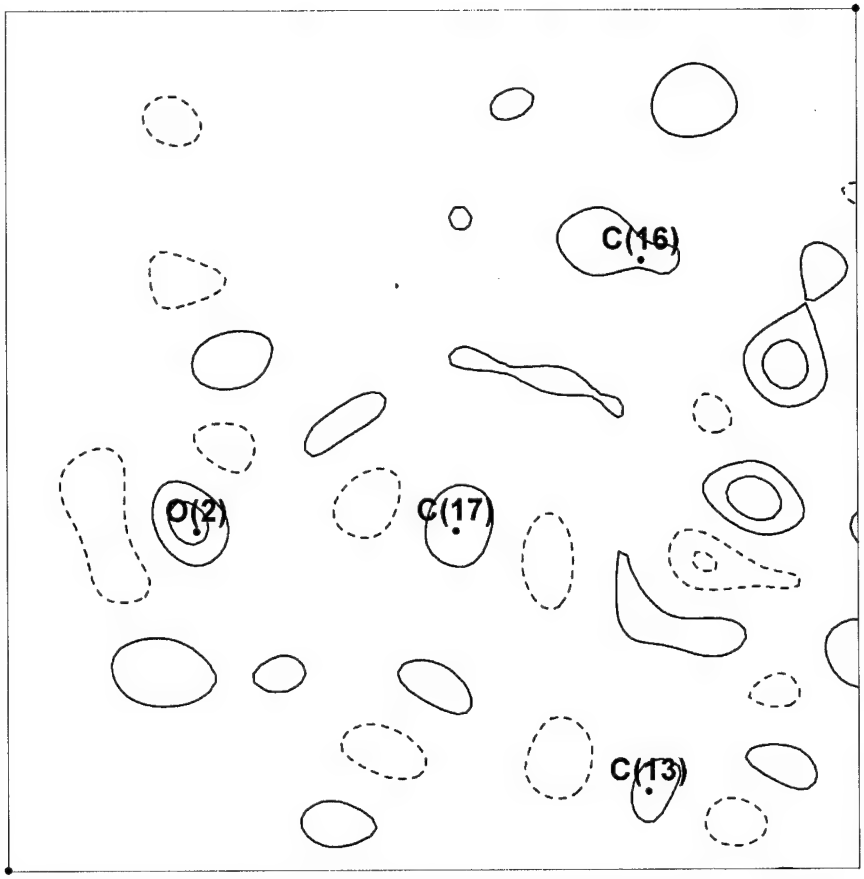

Figure 3b. The residual map in the O(2)-C(17)-C(16) plane.
Contour interval is 0.05 eÅ^{-3}.

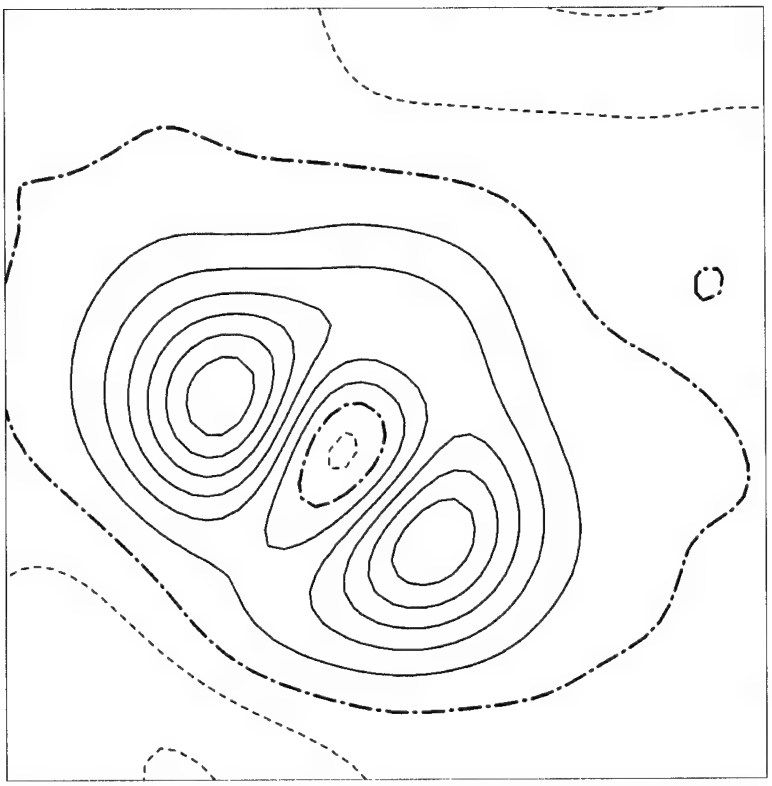

Figure 4a. Dynamic Fourier multipole electron density map showing the O(1) lone pairs. Contour interval is 0.05 $eÅ^{-3}$.

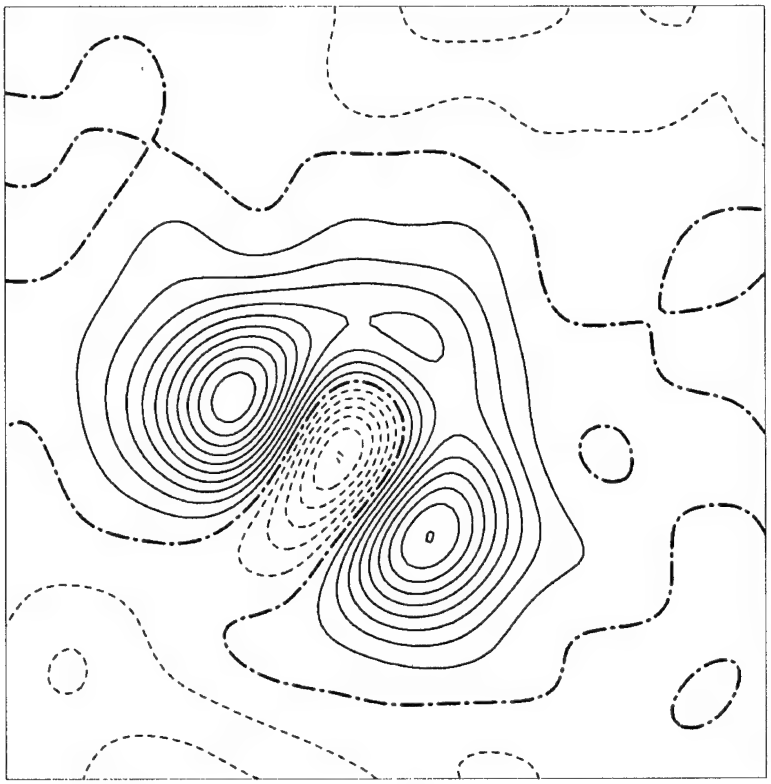

Figure 4b. Static Fourier multipole electron density map showing the O(1) lone pairs. Contour interval is 0.05 $e\text{Å}^{-3}$.

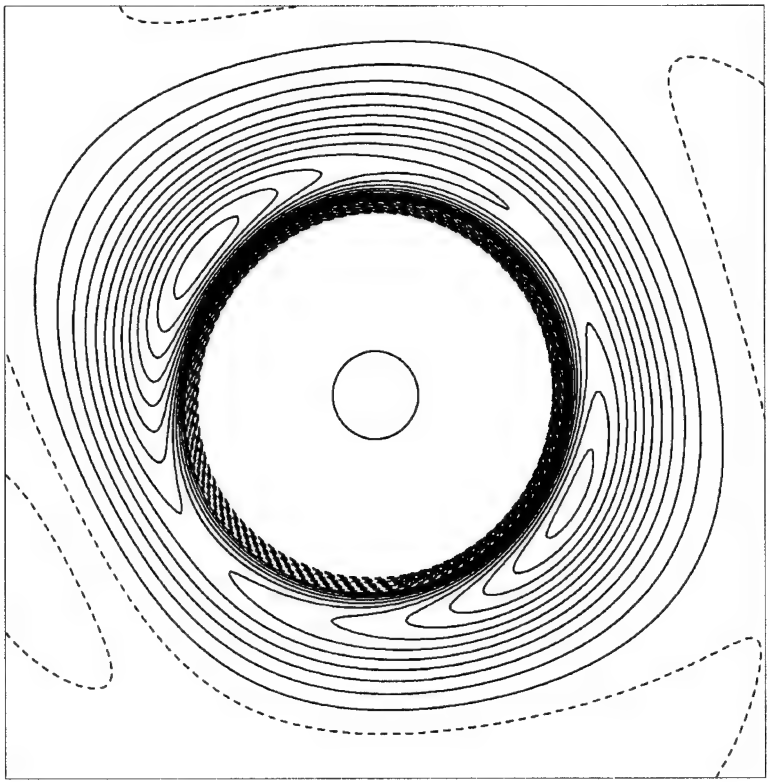

Figure 4c. The Laplacian of the electron density showing the O(1) lone pairs. Contours are from –130 to 130 eÅ^{-5} with interval 10 eÅ^{-3}.

(3,+3) minimum critical points in the Laplacian around the O(1) atom. These points reflect two Laplacian minima accosiated with O(1) lone pairs.

x	y	z	$\nabla^2\rho$, eÅ^{-5}
-1.3160	-0.7855	-0.3193	-120.2
-1.3909	-0.7981	-0.3139	-116.6

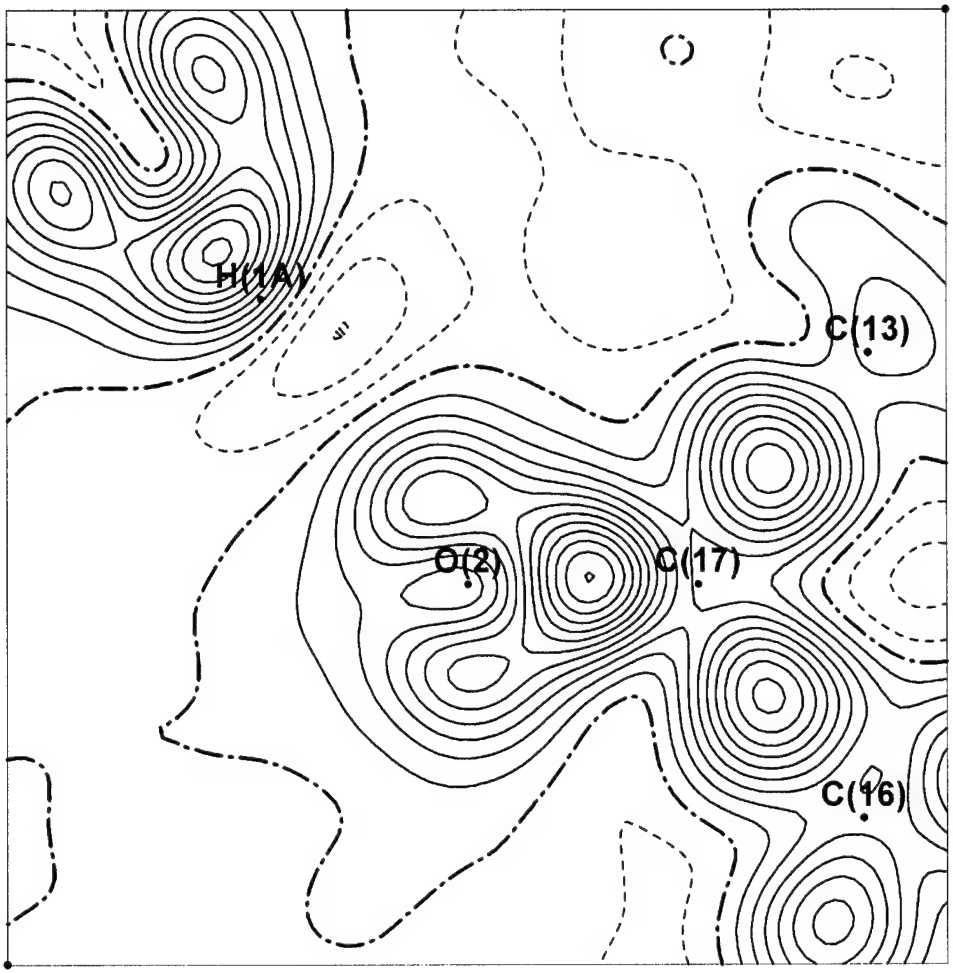

Figure 5a. The dynamic Fourier multipole electron density map in the O(2)-C(17)-$H(1A)_{next\_molecule}$ plane. The contour interval is 0.05 $eÅ^{-3}$. The hydrogen bonding region is shown.

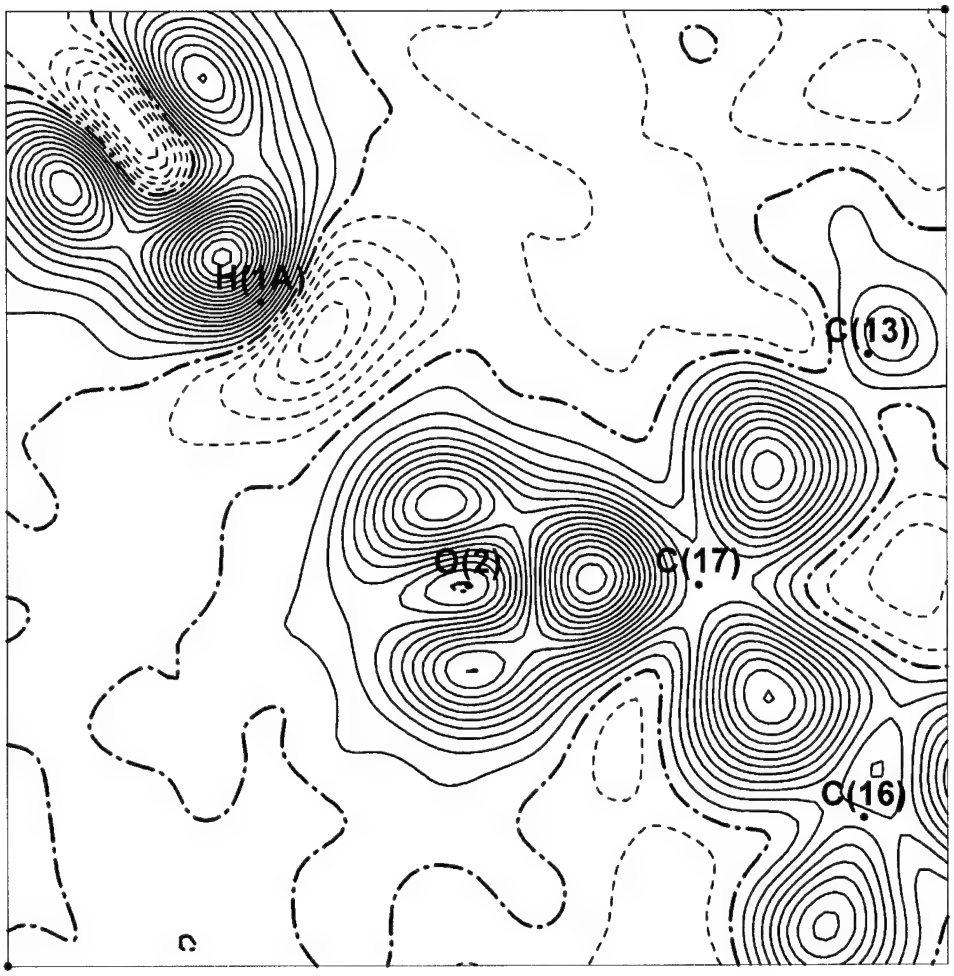

Figure 5b. The static Fourier multipole electron density map in the O(2)-C(17)-$H(1A)_{next\_molecule}$ plane. The contour interval is 0.05 $eÅ^{-3}$. The hydrogen bonding region is shown.

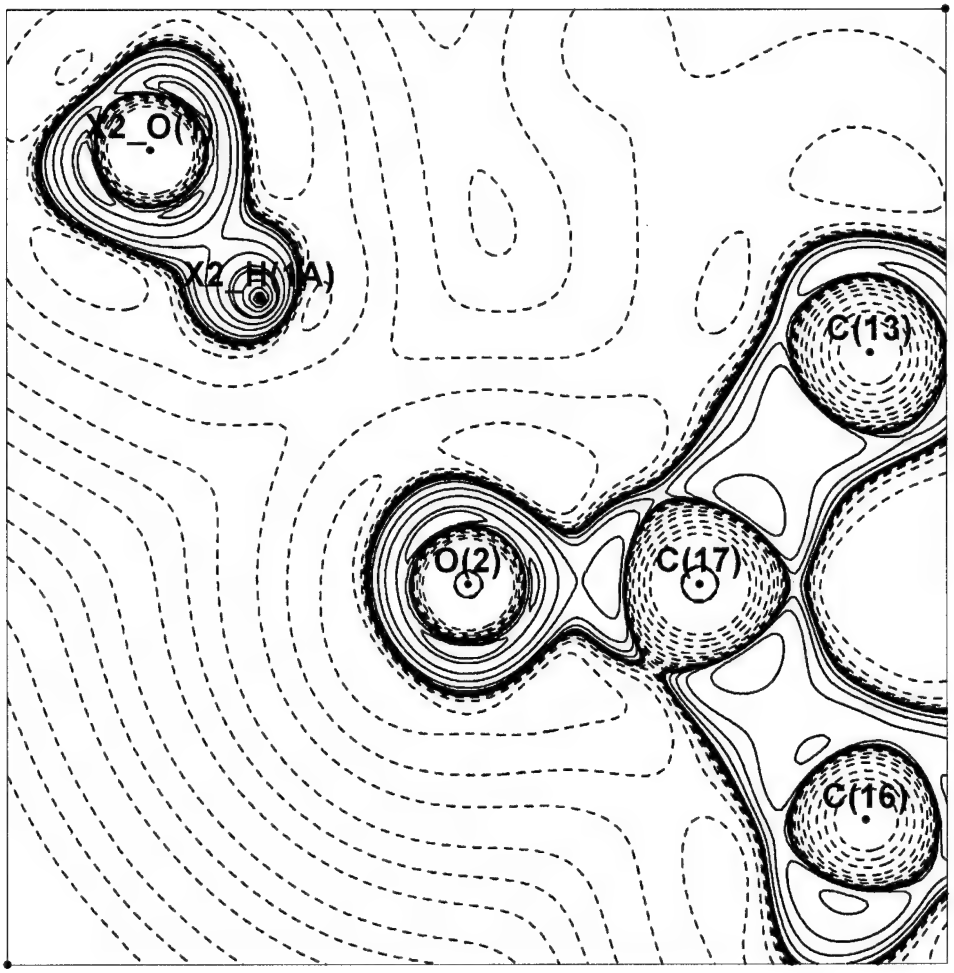

Figure 5c. The Laplacian of the electron density map in the $O(2)\text{-}C(17)\text{-}H(1A)_{next\_molecule}$ plane. The contour interval is 2,4,8 x 10^{-3-+3} eÅ^{-5} plus 100 eÅ^{-5} contour. The hydrogen bonding region is shown.

The (3,-1) bond critical points in the estrone crystal.

Bond		f	del2f	Rij	d1	d2	ellip
				Hessian Eigenvalues			
O(1)	-C(3)	2.128(17)	-22.849(77)	1.3699	0.8687	0.5011	
				-16.62	-15.70	9.48	0.06
O(1)	-H(1A)	2.669(116)	-59.134(1000)	0.9671	0.7522	0.2149	
				-46.46	-45.05	32.37	0.03
O(2)	-C(17)	2.913(22)	-12.730(144)	1.2241	0.8171	0.4070	
				-27.00	-26.48	40.75	0.02
O(2)	-X2_H(1A)	0.182(73)	2.369(137)	1.8539	1.2475	0.6064	
				-1.18	-1.12	4.67	0.05
C(1)	-C(2)	2.193(12)	-21.895(34)	1.3935	0.6485	0.7450	
				-14.52	-13.45	6.08	0.08
C(1)	-C(10)	2.191(15)	-21.866(41)	1.4058	0.6923	0.7135	
				-15.62	-13.14	6.90	0.19
C(1)	-H(1)	1.994(92)	-19.166(313)	1.0832	0.6547	0.4285	
				-17.77	-15.89	14.49	0.12
C(2)	-C(3)	2.269(14)	-23.462(38)	1.3987	0.6897	0.7089	
				-15.97	-14.39	6.90	0.11
C(2)	-H(2)	1.974(75)	-20.394(253)	1.0831	0.6546	0.4285	
				-17.87	-16.09	13.56	0.11
C(3)	-C(4)	2.291(14)	-25.008(37)	1.3969	0.7006	0.6963	
				-17.16	-14.32	6.47	0.20
C(4)	-C(5)	2.161(14)	-20.909(40)	1.4034	0.6505	0.7529	
				-14.59	-12.88	6.56	0.13
C(4)	-H(4)	1.943(82)	-20.414(281)	1.0831	0.6521	0.4310	
				-17.16	-16.51	13.25	0.04
C(5)	-C(6)	1.807(14)	-14.477(38)	1.5192	0.7928	0.7264	
				-11.85	-11.00	8.37	0.08
C(5)	-C(10)	2.140(15)	-21.026(52)	1.4120	0.6668	0.7451	
				-14.91	-13.24	7.13	0.13
C(6)	-C(7)	1.767(12)	-13.974(31)	1.5310	0.7622	0.7687	
				-11.55	-10.63	8.21	0.09
C(6)	-H(6A)	1.835(61)	-17.158(182)	1.0922	0.6344	0.4578	
				-15.17	-14.70	12.72	0.03
C(6)	-H(6B)	1.829(14)	-16.441(51)	1.0922	0.6366	0.4556	
				-15.28	-14.13	12.97	0.08
C(7)	-C(8)	1.717(12)	-12.733(33)	1.5272	0.7334	0.7938	
				-10.61	-10.24	8.11	0.04
C(7)	-H(7A)	1.949(59)	-19.054(185)	1.0923	0.6447	0.4475	
				-17.04	-15.46	13.44	0.10
C(7)	-H(7B)	1.873(14)	-16.504(51)	1.0921	0.6457	0.4464	
				-15.74	-14.80	14.04	0.06
C(8)	-C(9)	1.708(12)	-13.492(30)	1.5463	0.7668	0.7795	
				-11.45	-10.11	8.06	0.13
C(8)	-C(14)	1.791(13)	-15.780(32)	1.5249	0.7587	0.7662	
				-12.24	-11.35	7.81	0.08
C(8)	-H(8)	1.966(88)	-20.355(275)	1.0995	0.6504	0.4491	
				-17.16	-16.46	13.26	0.04

C(9)	-C(10)	1.718(13)	-14.351(37)	1.5278	0.7474	0.7804	
				-11.47	-11.01	8.12	0.04
C(9)	-C(11)	1.693(12)	-12.141(32)	1.5417	0.8041	0.7376	
				-10.58	-10.00	8.44	0.06
C(9)	-H(9)	1.962(80)	-20.120(222)	1.0999	0.6184	0.4815	
				-16.02	-15.24	11.13	0.05
C(11)	-C(12)	1.702(12)	-13.554(32)	1.5445	0.7764	0.7681	
				-11.03	-10.65	8.13	0.04
C(11)	-H(11A)	1.872(65)	-17.184(226)	1.0923	0.6670	0.4254	
				-16.61	-15.39	14.82	0.08
C(11)	-H(11B)	1.888(14)	-17.405(50)	1.0927	0.6703	0.4224	
				-16.82	-15.66	15.08	0.07
C(12)	-C(13)	1.781(12)	-15.139(34)	1.5272	0.7660	0.7612	
				-12.42	-10.73	8.01	0.16
C(12)	-H(12A)	1.908(55)	-18.213(170)	1.0922	0.6317	0.4605	
				-16.57	-14.45	12.81	0.15
C(12)	-H(12B)	1.905(14)	-17.500(53)	1.0921	0.6322	0.4599	
				-15.97	-14.42	12.89	0.11
C(13)	-C(14)	1.662(11)	-12.633(33)	1.5444	0.8016	0.7428	
				-10.50	-10.08	7.95	0.04
C(13)	-C(17)	1.786(13)	-15.569(41)	1.5180	0.7252	0.7927	
				-12.04	-11.64	8.12	0.03
C(13)	-C(18)	1.700(13)	-13.624(34)	1.5475	0.8162	0.7314	
				-11.00	-10.63	8.01	0.04
C(14)	-C(15)	1.712(13)	-12.844(33)	1.5409	0.7822	0.7587	
				-10.81	-10.39	8.36	0.04
C(14)	-H(14)	1.975(73)	-23.180(208)	1.0992	0.6150	0.4842	
				-16.70	-16.27	9.80	0.03
C(15)	-C(16)	1.674(13)	-12.768(33)	1.5499	0.7390	0.8109	
				-11.15	-10.03	8.42	0.11
C(15)	-H(15A)	1.857(65)	-14.108(227)	1.0924	0.6784	0.4140	
				-15.75	-15.05	16.70	0.05
C(15)	-H(15B)	1.847(15)	-14.898(51)	1.0921	0.6730	0.4191	
				-16.49	-14.54	16.13	0.13
C(16)	-C(17)	1.813(14)	-15.402(37)	1.5286	0.7264	0.8022	
				-12.08	-11.97	8.65	0.01
C(16)	-H(16A)	1.920(60)	-19.765(177)	1.0922	0.6327	0.4595	
				-16.60	-15.25	12.08	0.09
C(16)	-H(16B)	1.993(14)	-21.179(52)	1.0940	0.6410	0.4530	
				-17.58	-15.98	12.38	0.10
C(18)	-H(18A)	1.899(59)	-16.059(183)	1.0591	0.6195	0.4396	
				-16.23	-14.12	14.29	0.15
C(18)	-H(18B)	1.864(12)	-14.601(52)	1.0591	0.6169	0.4422	
				-15.16	-13.46	14.02	0.13
C(18)	-H(18C)	1.878(12)	-14.871(51)	1.0595	0.6195	0.4400	
				-15.60	-13.62	14.35	0.15

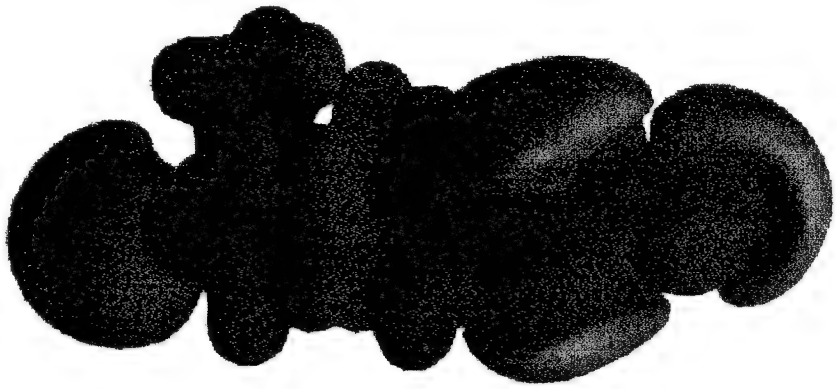

Figure 6. The electrostatic potential of the estrone molecule. Surfaces are +0.5 $eÅ^{-1}$ (blue) and –0.15 $eÅ^{-1}$ (red).

The multipole population parameters for the non-hydrogen atoms in estrone

Atom	P_v	κ'	κ''	D1+	D1-	D0	Q0	Q1+	Q1-	Q2+	Q2-	O0	O1+	O1-
O(1)	6.4184	0.9605	0.8732	-0.0094	0.0028	-0.0065	0.1163	-0.0092	0.0006	-0.0139	-0.0047	0.0229	0.0362	-0.0575
O(2)	6.2740	0.9771	0.8630	-0.0301	-0.0038	0.0051	-0.1364	0.0211	-0.0101	-0.0606	0.0238	-0.0105	0.0058	-0.0017
C(1)	4.2794	0.9552	0.7712	-0.0987	-0.0124	-0.0303	-0.2752	0.1253	-0.0323	-0.0521	0.0102	0.0103	-0.0173	0.0084
C(2)	4.4375	0.9552	0.7712	-0.0547	0.0629	0.0292	-0.3250	0.0371	-0.0825	0.0157	-0.0179	0.0451	-0.0319	0.0055
C(3)	3.7663	0.9844	0.8112	0.0032	0.0639	-0.0058	-0.2626	0.0219	-0.031	0.0452	-0.0932	-0.0205	0.0729	0.1016
C(4)	4.2846	0.9552	0.7712	-0.0829	0.0345	-0.0028	-0.2843	-0.0266	-0.0316	-0.0070	-0.0294	0.0241	0.1023	-0.0779
C(5)	4.2047	0.9567	0.8476	-0.0525	0.0672	-0.0318	-0.2366	-0.0603	0.0455	-0.0470	0.0063	0.0436	0.0115	-0.0520
C(6)	4.3544	0.9532	0.7973	-0.0249	0.0218	0.0157	-0.0462	0.0292	-0.0113	0.0173	-0.0185	0.0478	-0.0594	0.0245
C(7)	4.4117	0.9532	0.7973	-0.0905	0.0210	-0.0142	-0.0815	-0.0411	0.0612	0.0113	0.0369	-0.0166	0.0419	0.0494
C(8)	4.3339	0.9532	0.7973	0.0182	-0.0137	0.0150	0.0414	-0.0088	-0.0358	0.0076	0.0682	-0.0672	-0.0115	0.0556
C(9)	4.3135	0.9532	0.7973	-0.0918	-0.0315	-0.0291	0.0162	-0.0402	-0.0109	0.1001	-0.0192	0.0315	-0.0350	-0.0083
C(10)	4.1575	0.9567	0.8476	0.0010	0.0602	0.0721	-0.2216	0.0455	0.0785	0.0161	-0.0864	-0.0372	-0.0067	0.0312
C(11)	4.4237	0.9532	0.7973	-0.0755	0.0614	-0.0402	-0.0072	0.0026	0.0988	0.0762	0.0149	0.0052	0.0378	-0.0115
C(12)	4.3349	0.9532	0.7973	-0.0517	-0.0149	-0.0084	-0.0326	-0.0372	0.0149	0.0869	0.0182	0.0104	0.0717	-0.0216
C(13)	4.2497	0.9532	0.7973	-0.0146	0.0252	0.0166	0.0513	-0.0674	0.0175	-0.0330	0.0433	-0.0448	-0.0502	-0.0495
C(14)	4.0905	0.9532	0.7973	-0.0563	0.0512	0.0383	-0.0429	-0.0639	0.0135	-0.0699	0.0255	0.0408	0.0164	0.0010
C(15)	4.5093	0.9532	0.7973	-0.1772	0.0368	-0.0202	-0.0901	-0.0314	0.0906	0.0964	0.0105	-0.0278	-0.0391	0.0404
C(16)	4.4526)	0.9532	0.7973	-0.0252	0.0287	-0.0683	-0.0511	-0.0033	0.0025	0.0170	0.0214	0.0426	-0.0260	-0.0878
C(17)	4.0874	0.9793	0.8526	-0.0667	-0.0721	0.0088	-0.2910	0.0322	0.0298	-0.0798	0.0723	-0.0105	-0.0273	0.0417
C(18)	4.4600	0.9532	0.7973	0.1442	0.1494	-0.0717	0.0411	-0.0116	0.0037	-0.0096	-0.0881	-0.0636	-0.1116	-0.1525

(continued)

Atom	O2+	O2-	O3+	O3-	H0	H1+	H1-	H2+	H2-	H3+	H3-	H4+	H4-
O(1)	-0.0184	-0.0023	0.1121	-0.0111	0.0222	0.0314	-0.0164	0.0142	-0.0570	0.0315	0.0257	0.0324	0.0475
O(2)	0.0171	-0.0096	0.0500	-0.0147	0.0660	0.0061	-0.0043	-0.0176	-0.0451	-0.0217	0.0102	0.0237	-0.0190
C(1)	0.0356	-0.0619	0.3968	0.0853	0.0408	-0.0974	0.0804	-0.0197	-0.0192	-0.0623	0.0410	-0.0791	0.0504
C(2)	-0.0290	0.0229	0.4780	-0.0036	0.0868	-0.0747	0.0146	-0.0323	0.0758	-0.0574	0.0341	-0.0837	0.0344
C(3)	0.0557	-0.0034	0.4756	0.0234	0.0394	0.0203	0.0662	0.0954	0.0032	0.0426	0.0010	-0.0062	-0.0224
C(4)	0.0113	0.0482	0.4175	-0.0030	0.1128	0.0157	-0.0612	0.0868	0.0452	-0.0640	0.0294	-0.1145	0.0531
C(5)	-0.0326	-0.0319	0.3789	-0.0011	0.0780	-0.0444	-0.0405	0.0213	0.0626	-0.0572	0.0050	-0.0421	0.0265
C(6)	-0.0035	-0.4626	-0.0456	0.0097	-0.2044	0.0267	0.0112	-0.0329	-0.0251	0.0301	0.0439	-0.0605	0.0426
C(7)	-0.0072	-0.4316	-0.0520	0.0275	-0.2003	0.0289	0.0266	0.0182	0.0034	0.0546	0.1088	-0.0471	0.0024
C(8)	-0.0035	0.4666	-0.0003	-0.0140	-0.2974	0.0195	-0.0568	0.0080	-0.0077	0.0071	-0.0778	-0.1052	0.0416
C(9)	0.0859	-0.4763	0.0036	0.0617	-0.1985	-0.0348	0.0540	0.0616	-0.0313	-0.0794	0.0023	-0.1768	-0.1168
C(10)	-0.0091	-0.0445	0.3532	0.0370	0.0882	-0.0623	-0.0113	0.0149	0.0181	0.0115	0.0099	0.0024	0.0188
C(11)	-0.0111	-0.3846	-0.0666	-0.0422	-0.0895	0.0350	-0.0214	0.0300	0.0471	0.1087	-0.0425	-0.0447	0.0185
C(12)	-0.0166	-0.4309	-0.0413	-0.0252	-0.1147	0.0868	-0.0215	-0.0647	-0.0253	0.0193	-0.0784	-0.1276	-0.0223
C(13)	0.0823	0.4474	-0.0573	0.0188	-0.2513	0.0020	-0.0698	0.1336	-0.0481	-0.0814	-0.0744	-0.1422	0.0945
C(14)	0.1395	-0.3972	-0.0346	0.0280	-0.2245	0.1045	0.0201	-0.0071	0.0109	0.0023	0.0392	-0.0825	-0.0487
C(15)	0.0192	-0.4247	-0.0705	-0.0205	-0.1204	-0.1298	0.0312	-0.0067	-0.0006	-0.0299	-0.0142	-0.0530	0.0605
C(16)	0.0304	-0.4580	-0.0499	0.0537	-0.1858	-0.0183	-0.0047	-0.1146	0.0140	-0.0100	0.0111	-0.1016	-0.0674
C(17)	-0.0210	0.0247	0.4198	-0.1109	0.0335	-0.0970	-0.0166	0.0542	0.0111	0.0680	-0.0429	0.0345	0.0521
C(18)	-0.0367	0.3271	0.0065	0.03428	0.0143	-0.0584	0.0049	0.0259	0.0124	0.0661	0.0182	-0.0075	-0.0056

The multipole population parameters for hydrogen atoms in estrone

Atom	H(1A)	H(1)	H(2)	H(4)	H(6A)	H(6B)	H(7A)	H(7B)	H(8)	H(9)	H(11A)
P_v	0.7684	0.7024	0.6562	0.6705	0.7277	0.7277	0.7314	0.7314	0.7441	0.7720	0.7072
κ'	1.2031	1.4278	1.4278	1.4278	1.4278	1.4278	1.4278	1.4278	1.4278	1.4278	1.4278
κ''	1.3496	1.2774	1.2774	1.2774	1.2774	1.2774	1.2774	1.2774	1.2774	1.2774	1.2774
D1+	-0.0215	-0.0384	-0.0238	-0.0009	-0.0130	-0.0130	0.0244	0.0244	0.0204	0.0135	0.0219
D1-	0.0016	-0.0030	-0.0292	-0.0432	-0.0119	-0.0119	-0.0338	-0.0338	-0.0121	0.0097	-0.0207
D0	0.1855	0.1549	0.1751	0.1492	0.1558	0.1558	0.1523	0.1523	0.1417	0.2009	0.1090
Q0	0.0716	0.0395	0.0461	0.0733	-0.0225	-0.0225	0.0013	0.0013	0.0328	0.0102	0.0872
Q1+	0.0129	-	-	-	-	-	-	-	-	-	-
Q1-	-0.0154	-	-	-	-	-	-	-	-	-	-
Q2+	-0.0135	-	-	-	-	-	-	-	-	-	-
Q2-	0.0012	-	-	-	-	-	-	-	-	-	-

(continued)

Atom	H(11B)	H(12A)	H(12B)	H(14)	H(15A)	H(15B)	H(16A)	H(16B)	H(18A)	H(18B)	H(18C)
P_v	0.7072	0.7666	0.7666	0.7715	0.7032	0.7032	0.7155	0.7155	0.7895	0.7895	0.7895
κ'	1.4278	1.4278	1.4278	1.4278	1.4278	1.4278	1.4278	1.4278	1.4278	1.4278	1.4278
κ''	1.2774	1.2774	1.2774	1.2774	1.2774	1.2774	1.2774	1.2774	1.2774	1.2774	1.2774
D1+	0.0219	0.0252	0.0252	0.0050	-0.0323	-0.0323	-0.0108	-0.0108	0.0614	0.0614	0.0614
D1-	-0.0207	-0.0089	-0.0089	-0.0263	-0.0460	-0.0460	-0.0205	-0.0205	-0.0183	-0.0183	-0.0183
D0	0.1090	0.1564	0.1564	0.1515	0.1050	0.1050	0.1795	0.1795	0.1037	0.1037	0.1037
Q0	0.0872	0.0544	0.0544	0.1805	-0.0022	-0.0022	0.0552	0.0552	0.0231	0.0231	0.0231

Appendix F.

Charge density and electrostatic potential study on estrogen molecules:

3, 16α, 17β - Estriol

Charge density and electrostatic potential study on estrogen molecules: 16α, 17β - Estriol

Abstract

The measurements of the electron density distribution of the principal members of the estrogen family, the derivatives estriol, estradiol and estrone are now in progress. As a part of our study, the electron density distribution of 16α,17β-estriol ($C_{18}H_{24}O_3$) was determined from the high-resolution single crystal X-ray diffraction measurements at 100 K. Estriol crystallizes with two molecules in the asymmetric unit. Intensity data were collected using SMART 2K CCD area detector with Ag Kα radiation up to resolution $(\sin\theta/\lambda)_{max} = 1.29$ Å^{-1}. The structure was solved, and a conventional spherical atom refinement was carried out. A multipole pseudo atom refinement was then performed using the program XD. The electron density at the critical point of aromatic C–C bonds are larger than the other ring systems in the molecule. The electrostatic potential has been calculated for both molecules removed from the crystal lattice. Strong electro negative regions were found in the vicinity of the oxygen atoms of the 16α, 17β regions of both molecules. A small net negative electrostatic potential around 3-hydroxyl regions in both molecules may be related to low binding affinity of estriol. Net atomic charges were calculated from the kappa refinement. A group charge calculation indicates that the central region is close to neutral, but the head and tail regions form charged units. The topological analysis of the hydrogen bonds indicates the strength of the intermolecular interactions.

Introduction

In the recent years much attention has been paid on estrogen research[1]. The major role of estrogen molecules in the body influences the growth, development, and behavior, and affect many other body parts such as tissues, skin, bone, liver. Importantly, this family of steroid hormones regulates and sustains female sexual development and reproductive function[2a]. In other words, it stimulates tissue growth by promoting cell proliferation (DNA synthesis and cell division) in the female sex organs (breast, uterus)[2b]. Subtle changes in the structure of the estrogen molecules affect their chemical/biological behavior and can result in the development of growth inhibitors for tumors. For example, moving the hydroxy group from C(3) (estradiol)[3] to one of the adjacent C-atoms can change the carcinostatic potentials from agonistic (estradiol) to inhibitory (2-and 4-hydroxy estratrien -17β-ol)[4,5]. In this way, more than 60% of all breast cancers are known to be hormone dependent, i.e.,

initiation and progress can be influenced by estrogens and related compounds. These molecules bind as ligands to the estrogen receptor and hereby initiate a series of events resulting in the activation or repression of selective genes. While most changes modify the affinity of the ligand for the estrogen receptor, this does not necessarily correlate with the stimulation ability of the transcription of estrogen responsive genes. Several articles focused on identification and characterization of receptor ligand binding affinities. A recent comparative QSAR analysis of estrogen receptor ligands generalizes the effect of different substituents in estrogen molecules; more importantly, the substituents which increase the electron density in the A-ring appear to increase the binding affinity, and the steric character of substituent and polar character reduce the ligand receptor binding affinity[6]. An extensive crystallographic structural study reports the conformational features of these molecules and proposing the possibilities of ligand binding[7,8]. The knowledge of receptor or receptor complex model is essentially important to understand the binding mechanism. In this context the structural analysis of ligand binding domain (LBD) of two estrogen receptors (α and β) complexed with various ligands [9-11] has been reported. These studies emphasize the agonist and antagonist effect of certain hormones and drugs with the receptor. Furthermore, molecular modeling of a series of estrogen molecules has been conducted suggesting that conformational flexibility is the important property of specific ligands for the estrogen receptor[12]. However, still the mechanism by which the ligands regulate the gene expression is currently unknown, but it has been suggested[13] that the differences in electrostatic potential (ESP) can contribute to the variation in the regulation of hormone dependent genes. This information can be obtained from studies of the electronic properties in estrogen derivatives.

An experimental multipole representation of the charge distribution has been becoming very successful method to determine the electrostatic properties and to investigate the intermolecular interactions. An interesting study on the determination of ESP from multipole moments shows the importance of multipole moments in the intermolecular interactions[14,15]. Currently, various quantum mechanical models are available to explore the charge distribution, molecular ESP and its topological characteristics using multipole model[16-19]. However, it is highly desirable for the model to include the effect of intermolecular interactions to understand the molecular recognition processes. The multipole model experimental electron density analysis of molecules by the X-ray diffraction methods includes this aspect. In the recent years, experimental multipole model results have been extensively analyzed to elucidate the electronic properties of atoms in molecules. A widely accepted Bader's theory[20] of "Atoms in Molecules" is a useful tool to obtain electronic properties such as electron density at the critical point, Laplacian of charge density (charge concentration or depletion), bond ellipticity, charges of atoms and the electrostatic potential, which, in turn, aid in the prediction of how this molecule might react with a given environment. Moreover, the hydrogen bond topology studies characterize the strength of

intermolecular interactions.

We have begun a systematic study of estrogen compounds by investigating crystals of the derivatives of the principal estrogens, estriol, estradiol and estrone. The first study in this series, on estra-1,3,5(10)-triene-3,16α,17β-triol, (see Figure 1) is reported here. Estriol is the one of the active estrogens found in the body. The main source of estriol is the placenta, which produces a large amount of estriol during pregnancy[21], while the other two estrogens are produced in comparatively small amounts. Estriol does not associated with the cancer activity in the female body but it protects this disease. Estriol has much less stimulating effect on the breast and utrine lining than estradiol and estrone. Receptor binding studies have indicated that estriol has low binding affinity to estrogen receptors and, in general, it has the shortest receptor occupancy. From the distinct biological characteristics of estriol over the other two estrogens (estrone and estradiol), it implies that these molecules must differ in some way in their electronic properties and/or physical properties. The knowledge of the properties of these estrogens may help to understand the detailed mechanism of estrogenic activity of these molecules. The commercially available estriol has been crystallized from acetonitrile. We have carried out the crystallographic structure and electron density analysis from the high resolution X-ray diffraction measurement.

Experimental Section

1. Data collection

Estriol has been crystallized from acetonitrile by slow evaporation at room temperature. The crystals were found to be colorless and prismatic. In order to find a sample with good reflection profiles, several crystals were examined on the diffractometer for the low and high angle scattering. A well shaped 0.48 x 0.26 x 0.24 mm size crystal was selected and mounted on a Bruker SMART 2K CCD diffractometer using graphite monochromatized Ag Kα (λ = 0.56089Å) radiation (50V, 35mA). As a preliminary check, a room temperature data set was collected for a hemisphere. Refinement of the structure from this data gave results comparable to the reported crystal structure[22]. Then, the crystal was cooled to 100 K using an Oxford Cryostream N_2 open flow cryostat. After cooling, no significant unit cell modification was observed and the unit cell was very stable over the period of the entire data collection.

Initially the orientation matrix and the unit cell parameters were obtained from least-squares refinement using 88 well centered reflections measured in three sets of matrix runs of each 20 frames. The low temperature cell obtained in this way was ~2 % smaller than that at room temperature. A full sphere of low and high angle reflection intensities were measured using two detector settings at 2θ = 0° and 2θ = -50°, using the ω scan method for different φ angles (0, 45, 90, 135, 180, 225, 270 and 315°).

The CCD detector was placed at 5.1 cm from the crystal to minimize the reflection overlap. A total of 600 frames were collected for each φ angle with a scan width of 0.3°. The frame times for low (40 sec) and high angles (160 sec) were picked after the careful observation of the most intense reflection, avoiding detector overflow, but utilizing the full dynamic range. The crystal decay was monitored by re-measuring the initial 50 frames at the end of each data collection, and it was found to be negligible. The data collection strategy was checked with the program ASTRO[24] incorporated into the software package SMART[25]. We obtained 100% coverage for a resolution of $(\sin\theta/\lambda)_{max} = 1.2$ Å^{-1} with good redundancy. A total of 9600 frames were collected over the period of two weeks.

2. Data reduction and averaging

The best unit cell and the orientation matrix were determined by thresholding [$I/\sigma(I) > 20$] of reflections from each run of the data set. This orientation matrix fits well with the entire reciprocal space observed. The data has been integrated and corrected for the background, Lorentz and polarization effects using the software's advanced integrating procedures SAINT[26]. The method of integration of the collected frames was as described by Kabch[26] for area detectors. During the integration the orientation matrix and unit cell were not allowed to vary. Appropriate three dimensional box sizes were used in low and high angle integrations to account for the $K\alpha_1$ and $K\alpha_2$ splitting in high order reflections. No absorption correction was applied because of the low value of the absorption coefficient (0.055 mm^{-1}). All the corrected reflection intensities were scaled and averaged based on the point group symmetry using the program SORTAV[27]. A total of 277952 reflections were measured up to $\sin\theta/\lambda = 1.29$ Å^{-1}. 43918 are unique reflections with an average redundancy of 6.2. Of these, 989 unique data were measured only once, 3028 twice and 39882 three or more times. We note that, in the complete set of unique reflections, 29528 reflections were found to be greater than $3\sigma(I)$. The internal agreement factors[27] based on the averaging of symmetry equivalent reflections are R1 = 0.044, R2 = 0.031, wR = 0.11 and S = 1.4. The unit cell parameters, data collection, averaging and other crystallographic parameters are summarized in Table 1.

3. Conventional refinement

The room temperature crystal structure[22] of 16α, 17β-estriol has been previously reported. We solved the 100 K low temperature structure by direct methods and the spherical atom least squares refinement was carried out using the program SHELXTL[28]. All the hydrogen atoms, except one, were located from a difference Fourier synthesis. In the least squares refinement, all non-hydrogen atoms were treated anisotropically, and the hydrogen atoms were isotropic. The refinement converged with all data to R = 0.058, wR = 0.151 GOF = 1.01. Comparison of F_o and F_c values of the largest

structure factors gave no indication of the effect of extinction in the data. A thermal ellipsoid diagram (Figure 2) shows the two molecules in the asymmetric unit and the standard atom numbering scheme.

4. Multipole refinement

In order to model the deformation electron density and explore the bond topological characteristics like $\rho(\mathbf{r})$, $\nabla^2\rho(\mathbf{r})$, bond ellipticity (ε), molecular electrostatic potential etc., a multipole aspherical atom refinement was carried out using the Hansen-Coppens[29] multipole formalism implemented in the program XD[30]. According to this formalism, the total electron density of an aspherical atom is parameterized using an atom-centered multipole expansion

$$\rho_{atom}(\mathbf{r}) = P_c\,\rho_c(\mathbf{r}) + P_v\,\kappa^3\,\rho_v(\kappa\mathbf{r}) + \sum_{l=0}^{l_{max}} \kappa'^3_l\, R_l(\kappa'\mathbf{r}) \sum_{m=0}^{l} P_{lm\pm}\, d_{lm\pm}(\theta,\varphi)$$

The first two terms $\rho_c(\mathbf{r})$ and $\rho_v(\kappa\mathbf{r})$ are the spherically averaged Hartree-Fock atomic core and valence densities normalized for one electron; the third term describes the aspherical part of the pseudo atom; $R_l(\mathbf{r}) = [\alpha_l^{\,n_l+3}/(n_l+2)!]r^{nl}\,e^{-\alpha_l r}$ are the normalized radial distribution functions; α_l are the Hartree Fock optimized single zeta values; κ and κ' are radial expansion/contraction parameters which are optimized in the least-square refinement along with P_v and P_{lm}; P_{lm} are the multipole population coefficients; $d_{lm\pm}$ are density normalized real spherical harmonic angular functions and r, θ and φ are user defined local atom centered coordinates expressed in a polar coordinate system. In the multipole refinement, all carbon and oxygen atoms were allowed to expand up to the hexadecapole and the hydrogen atoms up to the dipole level. The κ and κ' parameters of all non-H atoms were refined, but hydrogen atoms κ' was fixed at 1.2.

In order to obtain accurate positional and thermal parameters for the non-hydrogen atoms, a high-angle refinement was carried out using the data with $\sin\theta/\lambda > 0.7$ Å^{-1}. All C-H distances were then reset to the neutron bond lengths [C_{sp2}–H = 1.083, C_{sp3}–H = 1.099(CH), 1.092(CH_2), 1.059(CH_3) and O–H = 0.967 Å] as reported in the International Tables[31]. This high-angle refinement converged without any significant change of scale factor, thus indicating the quality of the high angle data. The multipole refinement was carried out on the 25520 reflections [$I > 3\sigma(I)$] with the resolution $(\sin\theta/\lambda)_{max}$ = 1.1 Å^{-1}. The refinement strategy was as follows:

In the first step, Pv, κ and scale factor were refined; second step P_{lm}, κ'; third step xyz, U_{ij}, scale factor. Finally, xyz, U_{ij} and all electronic parameters were refined together. Since there are two molecules in the asymmetric unit, their multipole parameters were constrained to be equal at the beginning of the refinement, except the O–H group atoms as these are involved in the strong hydrogen bonding. In addition, to avoid the phase problem[32], all chemically equivalent atoms were initially constrained to be equal, but no site symmetry was imposed on any atoms in the molecules. At the later

stages of the refinement, the chemical atom constraints within the molecules were released, but not between the molecules. The residual index from the final refinement is given in Table 1. An attempt was made to refine the two molecules independently after the final refinement. This refinement did not give a meaningful result so we did not proceed further. The net atomic charges were calculated from a κ-refinement[33] (P_v, κ, and scale). During the refinements, the unit cell was constrained to be neutral and no charge transfer was allowed between the molecules. The featureless residual density maps of the two molecules (Figure 4) from the Fourier summation (F_o–F_{mul}) indicates the adequacy of the model refinement.

It is essential to test the physical significance and the correctness of the thermal parameters obtained from the model refinement. To accomplish this, Hirshfeld's[34] "rigid bond" test was performed for both the molecules leading to a satisfactory result. The maximum difference $\Delta_{A,B}$ between the atomic mean square displacement amplitudes along the interatomic vectors was 0.0013 Å.

Result and Discussion

1. Structural aspects

The report of the room temperature crystal structure[22] indicated significant conformational differences between the two molecules in the asymmetric unit. We observe some notable differences between the reported room temperature and current low temperature structure, so it is worth revisiting the structural analysis. Figure 2 shows the thermal ellipsoid representation of estriol with two independent molecules in the asymmetric unit obtained from the low temperature (100 K) measurement. The geometrical comparison of the two molecules explicitly indicates how the two molecules are conformationally different. On comparing the bond distances between the two molecules, no significant difference were observed, in contrast to the previous report[22]. The maximum deviation in the bond lengths of the ring (A-D) systems between the two molecules is 0.01 Å (Table 2). There is no evidence for C(2)–C(3) bond shortening in the A-ring systems as the room temperature structure reports[22]. The average C_{ar}–C_{ar} bond distances of A-ring atoms of molecule 1 and 2 are 1.3995 and 1.3990 Å respectively. The CH_3 group of the second molecule lies above the aromatic ring of the first producing distortion in the aromatic ring. This effect is reproduced here giving a folding in the A-ring of molecule 1 with a dihedral angle of 2.99°. There is no such effect in the second molecule where the A-ring system is planar (0.52°). There are differences in bond angles between the molecules 1 and 2 around the atoms C(9), C(13) and C(14) [Table 2]. However, we observe a maximum deviation of 2.5° compared to 3.9° as previously reported. The torsion angles in the Table 2 indicate the distortion of the B and C ring systems. The steric hindrance between the C-ring equatorial hydrogen atom at C(11) and the hydrogen

atom at C(1) produce different conformations of the B and C ring systems in the two molecules. Comparison of torsion angles between the molecules shows the major distortion appears at the head and tail part of the molecules (see Table 2). This is attributed to the different environment of intermolecular interactions of the molecules (1 and 2) with their neighbors. The relative strengths of the hydrogen bonds to O(3) in the two molecules was previously discussed on the basis of 0.04 Å difference in the C(16)–O(3) bond length. We observe less than 0.01 Å difference in this distance between molecules 1 and 2. Hydrogen bonding does, however, have an effect on the geometry of the hydroxyl groups. In the second molecule the 16α and 17β-hydroxyl C–O–H bond angles are systematically less compared with the first, the maximum difference being 8.8°. There is less of a differentiation in the 3-hydroxyl bonds, the deviation being 2.1°. The structure is characterized by strong hydrogen bonding. Figure 3 depicts the hydrogen-bonding environment of the two molecules in the asymmetric unit. Each hydroxyl group is involved in, at least, two hydrogen bonds. The hydrogen bonds O–H···O and O···H–O type of interactions in the molecules indicates the O-atoms behave as donor as well as acceptor. Moreover, O(1') has one additional hydrogen bond resulting in a tetrahedral coordination of the O-atom. The head to tail hydrogen bonds link the molecules into chains. The hydrogen bond geometrical parameters are given in Table 3.

2. Charge density distribution

The model static deformation density map in Figure 5 shows the bonding features of the different atoms in the estriol molecule. All chemical bonds show an increase in the electron density with respect to neutral spherical atoms as well as density associated with the lone pair regions of the oxygen atoms. The featureless residual electron density map was computed using the program XDFOUR[35] after the multipole refinement. The featureless residual maps (Figures 4a and b) of the two molecules in the asymmetric unit confirm the validity and the adequacy of the model refinement and the quality of the data set. The minimum and maximum residual density calculated for the molecules are 0.21, -0.29 (molecule1) and 0.22, -0.27eÅ^{-3} (molecule 2) respectively. As specified earlier, in the multipole refinement, the respective chemically equivalent ring atoms of the two molecules were constrained pair wise. No constraint was imposed on the hydroxyl groups, since they involved in strong hydrogen bonding. All further discussions are based on this constrained model.

In order to further characterize the interaction of atoms in a molecule, a topological analysis was performed based on Bader's theory[20] of "Atoms in Molecules" implemented in XDPROP[35]. This analysis includes the determination of electron density, $\rho(\mathbf{r}_c)$, at the bond critical point (CP), where $\nabla\rho(\mathbf{r}_c) = 0$, between the bonded atoms, its Laplacian, $\nabla^2\rho(\mathbf{r}_c)$, and bond ellipticity [$\varepsilon = (\lambda_1/\lambda_2)-1$]. Also, the eigenvalues of the second derivatives of $\rho(\mathbf{r}_c)$ was calculated to characterize the nature of the

bond critical point. The bond path analysis[36,37] gives information about the amount of deviation of the bond critical point from the internuclear axis, thus obtaining an additional measure of a strain. All these results, including the length of bond paths and internuclear distances, are listed in Table 4.

A-ring system: The topological analysis results reported in Table 4, such as $\lambda_1, \lambda_2, \lambda_3$, $\rho(\mathbf{r}_c)$, $\nabla^2\rho(\mathbf{r}_c)$, ε reveals the electronic insight into the estriol molecules. The magnitude of $\rho(\mathbf{r}_c)$ at the bond critical point is a clear indicator of the chemical bond strength. The electron density, $\rho(\mathbf{r}_c)$, at the critical points of the aromatic ring (C_{sp2}–C_{sp2}) bonds range from 2.04 to 2.19 eÅ^{-3}. The average value (2.1 eÅ^{-3}) is a typical value for aromatic bonds, but these values are 0.1 eÅ^{-3} smaller than in the reported p-nitrophenol[38]. The Laplacian, $\nabla^2\rho(\mathbf{r}_c)$, is a very sensitive parameter which identifies the areas where charge is concentrated (negative value) or depleted (positive value) in the bonding region. In this respect, we observe the maximum negative Laplacian in the A-ring bonds being –22.1(1) eÅ^{-5}, and this value appears less in the bonds linked to B ring atoms. However, the average value is –18.52 eÅ^{-5}, which is very close to an earlier observation for the benzene molecule[39]. The dispersion of bond ellipticity is attributed to the preferential charge accumulation in the bond. Bader's theory on ellipticity[20,40] emphasis the concept of the σ-π character of the bond. Explicitly, it is the measure of deviation of charge density from spherical symmetry (at the critical point). In this aspect the average value (0.18) of ellipticity of C_{sp2}–C_{sp2} bonds indicates the significant π (aromatic) character. This value is smaller than reported for the benzene ring bonds but completely agree with those in tris-annealed benzene[41]. The $\rho(\mathbf{r}_c)$'s in the C_{sp2}–H bonds range from 1.78(4) to 1.90(1) eÅ^{-3}, and this density is consistent with one would expect for the single C–H bonds. The Laplacian of the C(1)–H(1) bond is small compared with the other two C–H bonds, perhaps indicating weakening of the bond due to steric interactions with hydrogen atoms at C(11). The small ellipticity of C_{sp2}–H bonds is consistent with only a σ contribution in the single bonds.

B and C ring systems: The density of chemically equivalent C_{sp2}–C_{sp3} bonds in the B-ring are equal and their Laplacian's are very close (see Table 4). In both ring systems, the average values (1.70 and 1.67 eÅ^{-3}) of $\rho(\mathbf{r}_c)$'s in the C_{sp3}–C_{sp3} bonds are not very different and a similar trend appears for the Laplacian. The $\rho(\mathbf{r}_c)$'s and Laplacian for these bonds are significantly less than the aromatic ring system in agreement with their single bond character. In the C-ring the ellipticity of the bonds C(11)–C(12) and C(12)–C(13) are unexpectedly larger compared to the similar bonds having small values (see Table 4), indeed the values approach those of the aromatic ring. In all C_{sp3}–H (CH_2) bonds the density ranges from 1.64 to 1.86 eÅ^{-3} and C_{sp3}–H (CH) bonds 1.75 to 1.81 eÅ^{-3}. The average effect is same in both types of bonds. The Laplacian of these bonds is consistently smaller than for the C_{sp2}–H bonds. The maximum and minimum values are –8.9(2) and -18.6(1) eÅ^{-5}.

D-ring system: Having 5 members in the ring and due to the different hydrogen bonding

environments, this ring is highly strained in both molecules (1 and 2). Nevertheless, no significant difference was observed in the $\rho(\mathbf{r}_c)$'s at the bond critical points, except for C(14)–C(15) = 1.57 eÅ^{-3} implying a weakening of this bond. The average value of the Laplacian is -12.88 eÅ^{-5}. We observe the ellipticity of this five-member system being close to the B-ring bonds, and it is relatively small, consistent with the single bonds. The electron density (1.94 eÅ^{-3}) and the Laplacian of the C(16)–H(16) bond is surprisingly higher than the similar C(17)–H(17) bond in this ring (see Table 4).

C–O and O–H groups: In general, these groups play a significant role in the whole geometry of estrogen molecules. Especially the OH group perturbs the electron density of aromatic system and its electron density distribution is important in the ligand binding domain[13]. The $\rho_c(\mathbf{r})$'s of C_{sp2}–O [A-rings] bonds of both molecules (1 and 2) are larger than $\rho_c(\mathbf{r})$'s of the C_{sp3}–O bonds of D-ring, in agreement with conjugation of O(1) to the aromatic ring. The average values are 2.11 and 1.89 eÅ^{-3}. The Laplacians of the C_{sp2}–O bonds are not equal to C_{sp3}–O bonds, which indicates a strengthening of the bond to the aromatic ring. Whereas the ellipticity of the C(3)–O(1) bond in molecule 1 is a strong indicator of a π component of the bond, that in molecule 2 is closer to the value observed for the D ring. We attribute this to the difference in the hydrogen bonding in these two molecules. The small values of the ellipticity (0.05 - 0.1) in the C_{sp3}–O for both molecules indicate an unperturbed pure σ bond.

Bond path: In Table 4, Δd describes the deviation of bond critical point (CP) from an internuclear axis of a pair of bonded atoms in molecule. Essentially, the bond path[40,41] is a line which links two atoms by a maximum charge density. The bond path length significantly differs from internuclear distance and the amount of deviation indicates the extent at which the bond is strained. The distances d_1 and d_2 (see Table 4) are the bond path lengths between CP and the respective bonded atoms. Their inequality implies the degree of polarization of atom in the bond[38,42]. On inspecting all homonuclear atoms of the ring systems A through C, the minimum and maximum deviations are 0.004 and 0.03 Å. These deviations are smaller compared with the D-ring homonuclear bonds showing maximum deviation 0.044 Å. It confirms that the D-ring bonds are strained. However, this deviation is smaller than the highly strained C–C bonds of cyclopropane[43], bullvalence[44] (0.12 Å) and cubane[45] (0.17 Å) structures. The hetronuclear C–O bonds show marked differences in both molecules. The CP of C_{sp2}–O bond in the first molecule deviates by 0.03 Å from the internuclear axis, while in molecule 2 it lies very close (0.01 Å). In molecule 1, the deviation of BCP in the bonds C(17)–O(2) and C(16)–O(3) are 0.03 and 0.01 Å respectively. But these deviations are exactly opposite in the bonds C(17')–O(2') [0.01 Å] and C(16')–O(3') [0.04 Å] of molecule 2.

Topological properties of hydrogen bonds: Table 5 reports the hydrogen bond (O–H···O) topological properties of molecules 1 and 2. A (3,-1) hydrogen bond critical point's (HCP) which are located in

between H and O atoms of neighboring molecules. As we mentioned earlier, there are three hydrogen bonds exist in each molecule. Of the three hydrogen bonds from molecule 1, the two bonds [O(1)–H(1A)···O(3) and O(3)–H(3A)···O(1')] display approximately linear hydrogen bonding, 171.7, 170.5° respectively. The corresponding electron densities of these bonds at the HCP are similar with values of 0.23 and 0.20 eÅ^{-3}, respectively. Both of these bonds have a positive Laplacian $\nabla^2\rho(\mathbf{r}_c)$ at the HCP. This is characteristic of closed shell interactions[20] which are governed by the contraction of the electron density towards each of the interacting atoms. In molecule 2, we observe the similar electron densities and Laplacians for the bonds O(1')–H(1'A)··· O(3') and O(2')–H(2'A)···O(2'). The hydrogen bond O(2)–H(2A)···O(1) in molecule 1 shows a moderate electron density at the HCP (0.11 eÅ^{-3}) with a positive Laplacian. Although the hydrogen bond O(2')–H(2'A)···O(1') is approximately linear (169.2°), the electron density is very small at the CP (0.05 eÅ^{-3}). This may be attributed to the longer H(2'A)···O(1'A) distance and the fact that O(1'A) accepts one additional hydrogen bond. Further more, we have calculated bond path of H···O bonds. In H(1A)···O(3) bond the CP is not much deviated (0.056 Å) from internuclear axis and it is close (0.045 Å) to similar bond H(1'A)···O(3') in molecule 2. But in the 16α, 17β region of molecule 1, the H(2A)···O(1) deviates significantly (0.26 Å) compared with H(3A)···O(1') showing 0.05 Å. Similarly in molecule 2, the HCP's both for the bonds H(2'A)···O(1') and H(3'A)···O(2) are deviated by 0.36 and 0.1 Å respectively. This strange deviation in 17β regions of both molecules indicates that these are highly strained hydrogen bonds. Wide-angle deviations are larger than the reported value (0.12 Å) which was obtained from extensive electron density study on O–H···O hydrogen bonds[46].

3. Electrostatic potential

An additional important application of the multipole model is that it provides an opportunity to understand the chemical reactivity of molecules. That is to identify the places where nucleophilic or electrophilic attack may take place. The regions of the positive potential will attract nucleophilic reagents and the electronegative regions of the molecule will determine the approach of the electrophilic reagents. The electrostatic potential not only plays an important role in directing chemical attack, but also in the molecular recognition[47,48] (hormone receptor, drug receptor, enzyme-substrate interaction). This is because electrostatic forces are long-range interactions which determine the most stable geometrical orientation of two molecules. To investigate the aspect of the estrogen hormone receptor interaction, we have calculated the electrostatic potential around the molecules by the method of Su and Coppens[49] based on the populations obtained from the multipole refinement. The advantage of this method is that it allows to compute the ESP at points inside and outside the Van der Waals surface of the

charge distribution[30] and explore the topology of V(r)[50,51]. Generally, intermolecular potential involves the effect of electrostatic, induction, short range and dispersion interactions[52]. Although all these kinds of interactions alter the intermolecular interaction, the first one contributes significantly[53]. Thus, the molecules extracted from crystal lattice account for this many body effect. We have mapped the ESP of the isolated estriol single molecule and the fragments of the molecules which are involved in hydrogen bonding.

Figures 6a and 6b show contour plots (in the molecular mean plane) of the electrostatic potential of molecules 1 and 2 isolated from the crystal lattice. The view of positive contours around the aromatic rings are more diffuse than those of the saturated rings. In molecule 1, the positive contours are very compact around the atoms of the rings B, C, D compared with molecule 2. In Figure 6a, an empty (no ESP contours inside the ring) view of A-ring of molecule 1 indicates that the net electrostatic effect is zero, in comparison with the other ring systems showing the moderate potential values. The negative contours around the 16α, 17β oxygen atoms are much more pronounced than for the A-ring. The potential around molecule 1 is more symmetric than for molecule 2.

We have computed a 3D isosurface electrostatic potential of the pseudomolecule extracted from the crystal. In Figure 7, the anti-parallel view of two molecules reveals the difference of their ESP in the asymmetric unit. The positive equipotential (+0.5 $eÅ^{-1}$) surface shows the extension of ESP bound to the molecules 1 and 2. Especially, the bulk surface bound by aromatic ring of molecule 1 confirms the previous 2D observation. The negative equipotential surface indicates the amount of extended region for the value -0.15 $eÅ^{-1}$. More importantly, both the molecules have strong extended electronegative regions at the 16α, 17β-hydroxy groups, in contrast to the less electronegative regions observed at the 3-hydroxy groups. The negative region of molecule 1 exhibit spherically bounded ESP surface than in molecule 2. These distinct features can be attributed, at least to some extent, to the difference in polarization of such as weak and strong hydrogen bonded atoms. This kind of isosurface ESP analysis is becoming common in the biological and medicinal important molecules[54-56]. Finally, the view of the rich electronegative 16α, 17β hydroxyl region of two molecules together implies the diagonal orientation of ESP field vector[57-59] in the molecular geometry.

Furthermore, we have added the fragments of both molecules involved in strong hydrogen bonding to visualize the polarization. Figures 8a and b show the hydrogen bond environment of the O-atoms in molecules 1 and 2. Since ESP is attributed to the long-range electrostatic interaction, the hydrogen bonded atoms affect the existing potential around the molecule. The amount of variation of the ESP of the unperturbed molecules depends upon the direction and charge distribution of the two or more interacting molecules or fragments. The hydrogen bonded fragments of the neighboring molecules show the visual representation of polarization of hydrogen bonded atoms and the net effect of ESP in the inter

molecular region. Similar effects were observed in phosphorylethanolamine[56] crystal structure. Figure 8 emphasizes the net effect of ESP around each O–H groups of both molecules, after adding the hydrogen bonding fragments.

4. Net atomic charges

The net atomic charges (Table 6a) have been calculated from a κ-refinement (κ, P_v, scale). In this refinement the chemically equivalent atoms were constrained as described in the multipole refinement, and no charge transfer has been allowed between the molecule 1 and 2. Both molecules were kept neutral. All oxygen atoms carry significant negative charges in the range –0.63 to –0.87e. Similarly all hydroxyl hydrogen atoms carry high positive charges, approximately double the amount of charge of the other hydrogen atoms in the molecules. The charges of chemically equivalent aromatic atoms C(2) and C(3) are equal and they are much smaller than C(1), as expected. The equivalent C_{sp3} atoms C(6), C(7), C(11), and C(12) are carrying moderate charges and they are almost equal. A similar C_{sp3} (CH) kind of atoms C(8), C(9) and C(14) carrying small amount of charge except C(9). These charges are effectively larger than for the similar D-ring atoms C(16) and C(17) (see Table 6), this anomaly may be due to the different environment. The overall charge distribution of C- atoms in the ring systems A through D indicates that the aromatic A-ring and D-ring are holding lesser amount of charge compared to B and C ring systems. A group charge calculation (Table 6b) on both molecules indicates that the central regions are close to neutral, whereas the head and tails form charged units. Surprisingly, the 3-hydroxy (molecule 1) and 16α (molecule 2) regions are holding less negative charges (see Table 6b).

Conclusion

The present study on estriol gives an information on both the structural and electronic properties of the molecule. The differences in hydrogen bonding, molecular packing environment, and interamolecular steric effects are responsible for the small differences in the two molecules in the asymmetric unit. The significant differences reported for the room temperature structure were not confirmed here. The comparison of torsion angles between the two molecules shows that the major difference at the head and tail portions of the molecules may be attributed to the different hydrogen bonding environment, both molecules being involved in the strong hydrogen bonding.

The electronic information of A-ring system of the estrogen molecules is very important for the ligand receptor binding[13,6]. The electron densities at the CP of the aromatic C–C bonds are larger than for the C_{sp3}–C_{sp3} bonds of the B, C and D ring systems. The additional electron density accumulation in the aromatic bonds along with the ellipticity indicates a π contribution. The unconstrained refinement of

the hydroxyl groups between the two molecules shows differences in both C–O and O–H bond electron densities at the CP. The average C_{sp3}–O bond density is significantly less than C_{sp2}–O density. The charge accumulation in the O–H (16α,17β position) bond is slightly larger than in the 3-hydroxy O–H bond. Strong electronegative regions were found in the electrostatic potential maps at the vicinity of the oxygen atoms of the 16α,17β groups of both molecules. The extension of positive and negative contours explicitly indicates the electrostatic interaction with the neighboring molecules.

The hydrogen bonding O–H···O and O···H–O interaction at the head and tail portion of the molecule shows the possibility of having the positive and negative regions of the ligand binding domain of the receptor. The favored direction of alignment of the non-identical molecules together in the crystal lattice is along the direction of maximum negative ESP. The large electron density at the hydrogen bond CP's encourages the very strong nature of the hydrogen bonding in the estriol crystal.

Net atomic charges computed from the κ-refinement gave a reasonable distribution of charges. In the 16α,17β position, the oxygen atoms O(2), O(3) (molecule 1) and O(2'), O(3') (molecule 2) carry more negative charges than 3-hydroxy atoms O(1) and O(1').

To relate the results obtained from the electron density analysis and ESP with biological characteristics of estriol, the small negative ESP at the 3-hydroxy positions and the broad shape of negative ESP at the 16α,17β around O-atoms overlapping with the neighboring groups, and the conformational flexibility (i.e., two molecules arises in the asymmetric unit with different conformations) reduces the effective binding of molecules with the receptor. The first two of these results support the conclusion derived in isopotential study[13] in which the strong extended ESP at the 3-hydroxyl region is expected.

Thus, the way of representing and analyzing the experimental ESP brings out the approximate electrostatic characteristics of a molecule in the nonbonding environment. And the ESP extracted from the crystal lattice is suitable for the simulation of hormone-receptor interactions at different physiological situations.

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50. $V(r)= \Sigma_j Z_j / |r-R_j| - \int \rho(r)/ |r-r'| dr'$ Where R_j and Z_j are the position and charge of the j-th nucleus, respectively.

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Table 1. Crystal data and Experimental conditions[a]

Crystal Data	
Empirical formula	$C_{18}H_{24}O_3$
Formula weight	288.37
Crystal system	Monoclinic
Space group	$P2_1$
a (Å)	7.5077(4)
b (Å)	23.0809(12)
c (Å)	9.1632(5)
β (deg)	110.957(2)
V (Å^3)	1482.8
Z	4
F(000)	624
Dx (Mg/m^3)	1.292
μ (mm^{-1})	0.055
Data collection	
Diffractometer	Brukers SMART 2K CCD
Radiation, λ (Å)	Ag Kα, 0.56087
Scan method, width (deg)	ω-scan, 0.3
No. of reflections measured	278184
$\sin(\theta/\lambda)_{max}$ (Å^{-1})	1.29
R_{int}	0.042
No. of unique data	43918
Multipole refinement	
No. of relections ($F \geq 3\sigma$, $\sin(\theta/\lambda)_{max} = 1.1$ Å^{-1})	25520
R(F), wR(F)	0.032, 0.035
GOF	0.98
N_{obs}/N_{par}	26.6

[a] $R_{int} = \Sigma|I-I_{mean}|/\Sigma I$; $R(F)=\Sigma(||F_o|-|F_c||/\Sigma|F_o|)$; $wR(F)=(\Sigma(F_o-F_c)^2/\Sigma wF_o^2)^{1/2}$; $w=1/\sigma^2(F_o)$

Table 2. Selected geometrical parameters of molecule 1 and 2[a]

Bond lengths (Å)

bond	*m1*	*m2*
C(1)–C(2)	1.3938(8)	1.3962(7)
C(2)–C(3)	1.3952(8)	1.3936(7)
C(3)–C(4)	1.3939(7)	1.3921(7)
C(4)–C(5)	1.3991(7)	1.3978(6)
C(5)–C(10)	1.4084(7)	1.4111(7)
C(1)–C(10)	1.4064(7)	1.4034(7)
O(1)–C(3)	1.3693(8)	1.3785(7)
C(5)–C(6)	1.5146(7)	1.5154(7)
C(6)–C(7)	1.5255(7)	1.5250(7)
C(7)–C(8)	1.5293(7)	1.5264(7)
C(8)–C(9)	1.5444(7)	1.5424(6)
C(9)–C(10)	1.5278(7)	1.5253(6)
C(9)–C(11)	1.5388(7)	1.5408(7)
C(11)–C(12)	1.5409(7)	1.5441(7)
C(12)–C(13)	1.5325(7)	1.5313 (7)
C(13)–C(14)	1.5508(7)	1.5415(7)
C(13)–C(17)	1.5360(7)	1.5462(7)
C(13)–C(18)	1.5368(8)	1.5334(7)
C(14)–C(15)	1.5400(7)	1.5360(7)
C(14)–C(8)	1.5235(7)	1.5172(7)
C(15)–C(16)	1.5529(7)	1.5499(7)
C(16)–(17)	1.5413(7)	1.5463(7)
C(16)–O(3)	1.4387(9)	1.4278(8)
C(17)–O(2)	1.4293(7)	1.4168(8)

[a] *m1*-molecule 1 and *m2*-molecule 2

Bond angles (deg)

Bond	*m1*	*m2*
C(1)–C(2)–C(3)	119.3(1)	199.1(1)
O(1)–C(3)–C(2)	118.4(1)	118.1(1)
O(1)–C(3)–C(4)	121.9(1)	121.8(1)
C(2)–C(3)–C(4)	119.6(1)	120.0(1)
C(3)–C(4)–C(5)	121.0(1)	120.6(1)
C(4)–C(5)–C(6)	118.1(1)	117.2(1)
C(4)–C(5)–C(10)	120.3(1)	120.4(1)
C(6)–C(5)–C(10)	121.6(1)	122.4(1)
C(5)–C(6)–C(7)	113.1(1)	113.6(1)
C(6)–C(7)–C(8)	110.2(1)	110.7(1)
C(7)–C(8)–C(9)	109.0(1)	108.4(1)
C(7)–C(8)–C(14)	112.7(1)	111.9(1)
C(9)–C(8)–C(14)	107.8(1)	109.4(1)
C(8)–C(9)–C(10)	112.2(1)	109.9(1)
C(8)–C(9)–C(11)	111.3(1)	112.5(1)
C(10)–C(9)–C(11)	114.8(1)	114.3(1)
C(1)–C(10)–C(5)	117.6(1)	117.7(1)
C(1)–C(10)–C(9)	121.1(1)	121.8(1)
C(5)–C(10)–C(9)	121.0(1)	120.5(1)
C(9)–C(11)–C(12)	111.9(1)	112.7(1)
C(11)–C(12)–C(13)	111.4(1)	110.6(1)
C(12)–C(13)–C(14)	108.5(1)	108.4(1)
C(12)–C(13)–C(17)	115.4(1)	117.1(1)
C(12)–C(13)–C(18)	110.6(1)	109.8(1)
C(14)–C(13)–C(17)	97.6(1)	98.6(1)
C(14)–C(13)–C(18)	113.6(1)	113.5(1)
C(17)–C(13)–C(18)	110.7(1)	109.1(1)
C(8)–C(14)–C(13)	113.7(1)	113.8(1)
C(8)–C(14)–C(15)	120.6(1)	118.1(1)
C(13)–C(14)–C(15)	103.5(1)	103.8(1)
C(14)–C(15) –C(16)	104.0(1)	104.2(1)
O(3)–C(16)–C(15)	113.9(1)	113.1(1)
O(3)–C(16)–C(17)	111.6(1)	113.0(1)
C(15)–C(16)–C(17)	104.8(1)	105.6(1)
O(2)–C(17)–C(13)	119.7(1)	116.6(1)
O(2)–C(17)–C(16)	112.0(1)	110.2(1)
C(13)–C(17)–C(16)	104.6(1)	103.2(1)
C(3)–O(1)–H(1A)	110.4(2)	108.4(2)
C(17)–O(2) –H(2A)	112.7(2)	103.8(2)
C(16)–O(3)–H(3A)	116.9(1)	109.6(2)

Torsion angles (deg)

Bond	*m1*	*m2*
A-ring		
C(10)–C(1)–C(2)–C(3)	-0.5(2)	-0.5(2)
C(1)–C(2)–C(3)–C(4)	2.1(2)	0.8(2)
C(2)–C(3)–C(4)–C(5)	-2.1(2)	-0.3(2)
C(3)–C(4)–C(5)–C(10)	0.5(2)	-0.4(2)
C(4)–C(5)–C(10)–C(1)	1.1(2)	0.7(2)
C(5)–C(10)–C(1)–C(2)	-1.1(2)	-0.3(2)
B-ring		
C(10)–C(5)–C(6)–C(7)	-19.3(2)	-10.5(2)
C(5)–C(6)–C(7)–C(8)	48.4(2)	41.1(2)
C(6)–C(7)–C(8)–C(9)	-65.0(2)	-66.0(2)
C(7)–C(8)–C(9)–C(10)	50.7(2)	57.8(2)
C(8)–C(9)–C(10)–C(5)	-22.2(2)	-27.9(2)
C(9)–C(10)–C(5)–C(6)	6.2(2)	4.3(2)
C-ring		
C(8)–C(9)–C(11)–C(12)	56.2(2)	51.8(2)
C(9)–C(11)–C(12)–C(13)	-55.2(2)	-54.7(2)
C(11)–C(12)–C(13)–C(14)	54.4(2)	56.8(2)
C(12)–C(13)–C(14)–C(8)	-58.7(2)	-60.2(2)
C(13)–C(14)–C(8)–C(9)	59.3(2)	56.9(2)
C(14)–C(8)–C(9)–C(11)	-56.6(2)	-51.4(2)
D-ring		
C(13)–C(14)–C(15)–C(16)	-33.3(2)	-31.2(2)
C(14)–C(15)–C(16)–C(17)	4.2(2)	2.0(2)
C(15)–C(16)–C(17)–C(13)	26.7(2)	27.6(2)
C(16)–C(17)–C(13)–C(14)	-45.9(2)	-45.8(2)
C(17)–C(13)–C(14)–C(15)	48.6(2)	47.7(2)
C(13)–C(17)–C(16)–O(3)	150.4(2)	151.8(2)
C(15)–C(16)–C(17)–O(2)	157.7(2)	152.9(2)
C(13)–C(17)–O(2)–H(2A)	-4.7(2)	-78.1(2)
C(15)–C(16)–O(3)–H(3A)	84.4(2)	50.8(2)
C(2)–C(3)–O(1)–H(1A)	169.7(2)	-176.3(2)
C(4)–C(3)–O(1)–H(1A)	-8.5(2)	3.6(2)

Table 3. Hydrogen bonds[a]

bond	O–H (Å)	O···O (Å)	H···O (Å)	O–H···O (deg)
m1				
O(1)–H(1A)···O(3)[a]	0.97	2.646(2)	1.682(2)	171.7(1)
O(2)–H(2A)···O(1)[b]	0.97	2.773(2)	1.851(1)	158.6(1)
O(3)–H(3A)···O(1')[c]	0.97	2.890(1)	1.930(1)	170.5(1)
m2				
O(1')–H(1'A)···O(3')[d]	0.97	2.640(2)	1.684(1)	169.9(1)
O(2')–H(2'A)···O(1')[e]	0.97	2.884(1)	1.927(1)	169.2(1)
O(3')–H(3'A)···O(2)[f]	0.97	2.736(1)	1.857(1)	149.9(1)

[a] Symmetry codes: (a) -x+2, y-½, -z+1; (b) -x+1, y+½, -z+1; (c) x, y, z-1 ; (d) -x+1, y+½, -z+2; (e) -x+2, y-½, -z+2; (f) -x+1, y-½, -z+1

Table 4. Analysis of the properties of the bond critical points for the molecule 1 (first row) and 2 (second row)[a]

bond	λ_1	λ_2	λ_3	$\rho(r_c)$ (eÅ^{-3})	$\nabla^2\rho(r_c)$ (eÅ^{-5})	R_{ij} (Å)	d_1 (Å)	d_2 (Å)	ε	Δd (Å)
A-ring										
C(1)–C(2)	-15.07	-12.99	9.95	2.14(1)	-18.1(1)	1.3939	0.7040	0.6899	0.16	0.01
C(2)–C(3)	-16.61	-14.18	8.67	2.19(2)	-22.1(1)	1.3967	0.6846	0.7121	0.17	0.03
C(3)–C(4)	-15.88	-13.36	8.29	2.15(1)	-21.0(1)	1.3947	0.7607	0.6340	0.19	0.02
C(4)–C(5)	-14.72	-12.60	9.51	2.04(1)	-17.8(1)	1.3993	0.6975	0.7017	0.17	0.01
C(5)–C(10)	-14.47	-12.27	9.74	2.05(1)	-17.0(1)	1.4087	0.7253	0.6834	0.18	0.01
C(10)–C(1)	-13.89	-11.35	10.12	2.04(1)	-15.1(1)	1.4065	0.7349	0.6716	0.22	0.01
C(1)–H(1)	-15.65	-14.68	16.05	1.80(1)	-14.3(1)	1.0817	0.7067	0.3750	0.07	0.01
C(2)–H(2)	-17.65	-15.99	11.59	1.90(1)	-22.1(1)	1.0832	0.6889	0.3943	0.10	0.02
C(4)–H(4)	-16.16	-15.03	11.97	1.78(4)	-19.2(1)	1.0849	0.6950	0.3900	0.07	0.002
C(3)–O(1)	-18.17	-14.42	11.28	2.05(3)	-21.3(1)	1.3708	0.8343	0.5365	0.26	0.03
	-17.65	-16.46	12.08	2.16(2)	-22.0(1)	1.3787	0.8627	0.5159	0.07	0.01
O(1)–H(1A)	-43.38	-42.37	27.52	2.08(8)	-58.2(8)	0.9700	0.8205	0.1495	0.02	0.004
	-40.29	-39.52	31.58	2.18(8)	-48.2(7)	0.9661	0.7967	0.1694	0.02	0.004
B-ring										
C(5)–C(6)	-11.20	-10.55	10.64	1.71(1)	-11.1(1)	1.5148	0.7741	0.7408	0.06	0.01
C(6)–C(7)	-11.48	-10.65	10.97	1.74(1)	-11.2(1)	1.5258	0.7633	0.7625	0.08	0.02
C(7)–C(8)	-11.20	-10.26	10.40	1.67(1)	-11.1(1)	1.5293	0.7806	0.7487	0.09	0.004
C(8)–C(9)	-11.94	-11.08	9.82	1.71(1)	-13.2(1)	1.5453	0.7704	0.7749	0.08	0.03
C(9)–C(10)	-11.36	-10.41	10.20	1.69(1)	-11.6(1)	1.5284	0.7911	0.7373	0.09	0.02
C(6)–H(6A)	-15.34	-13.61	12.99	1.82(4)	-16.0(1)	1.0944	0.6649	0.4295	0.13	0.01
C(6)–H(6B)	-13.83	-13.29	18.21	1.64(4)	-8.9(2)	1.0919	0.7474	0.3446	0.04	0.02
C(7)–H(7A)	-17.50	-16.33	15.29	1.86(4)	-18.6(1)	1.0933	0.7508	0.3425	0.07	0.004
C(7)–H(7B)	-16.31	-15.14	14.93	1.83(4)	-16.5(1)	1.0922	0.7205	0.3717	0.08	0.01
C(8)–H(8)	-16.79	-15.76	15.69	1.76(4)	-16.9(2)	1.0990	0.7745	0.3245	0.07	0.01
C(9)–H(9)	-16.14	-15.65	14.21	1.81(4)	-17.6(1)	1.0984	0.7295	0.3688	0.0	0.01
C-ring										
C(9)–C(11)	-10.75	-10.54	10.25	1.65(2)	-11.0(1)	1.5389	0.7555	0.7834	0.02	0.01
C(11)–C(12)	-10.95	-9.56	10.61	1.63(1)	-9.9(1)	1.5410	0.7595	0.7816	0.14	0.01
C(12)–C(13)	-12.33	-10.71	9.98	1.73(1)	-13.1(1)	1.5328	0.7586	0.7742	0.15	0.02
C(13)–C(14)	-11.29	-10.42	9.46	1.62(1)	-12.3(1)	1.5510	0.7749	0.7761	0.08	0.01
C(14)–C(8)	-12.98	-11.80	8.96	1.73(1)	-15.8(1)	1.5236	0.7627	0.7609	0.10	0.01
C(11)–H(11A)	-14.98	-14.54	15.54	1.75(4)	-14.0(1)	1.0938	0.7228	0.3710	0.03	0.02
C(11)–H(11B)	-16.06	-15.38	14.43	1.80(4)	-17.0(1)	1.0909	0.7187	0.3722	0.04	0.01
C(12)–H(12A)	-15.92	-15.31	17.02	1.77(4)	-14.2(2)	1.0917	0.7602	0.3315	0.04	0.004
C(12)–H(12B)	-15.35	-14.45	13.31	1.79(4)	-16.5(1)	1.0901	0.6871	0.4031	0.06	0.01
C(14)–H(14)	-16.50	-16.13	15.31	1.75(4)	-17.3(2)	1.1011	0.7792	0.3219	0.02	0.02
D-ring										
C(14)–C(15)	-10.27	-10.19	10.12	1.57(1)	-10.4(1)	1.5409	0.7816	0.7593	0.01	0.03
C(15)–C(16)	-12.10	-11.18	9.38	1.71(1)	-13.9(1)	1.5544	0.7375	0.8169	0.08	0.035
C(16)–C(17)	-12.71	-12.07	9.51	1.79(1)	-15.3(1)	1.5416	0.7916	0.7499	0.05	0.014
C(17)–C(13)	-11.13	-10.28	9.56	1.65(1)	-11.9(1)	1.5386	0.7199	0.8187	0.08	0.044
C(15)–H(15A)	-17.40	-15.51	12.54	1.82(4)	-20.4(1)	1.0927	0.7242	0.3684	0.12	0.01
C(15)–H(15B)	-16.14	-15.14	16.09	1.68(5)	-15.2(2)	1.0948	0.7847	0.3101	0.07	0.02
C(16)–H(16)	-19.35	-18.60	13.23	1.94(5)	-24.7(2)	1.0968	0.7741	0.3227	0.04	0.01
C(17)–H(17)	-17.41	-16.91	15.27	1.78(4)	-19.1(2)	1.1009	0.7915	0.3094	0.03	0.014
C(17)–O(2)	-14.85	-14.05	13.75	1.96(2)	-15.2(1)	1.4308	0.8536	0.5772	0.06	0.03
	-13.95	-12.67	14.94	1.91(3)	-11.7(1)	1.4170	0.8319	0.5852	0.10	0.01
O(2)–H(2A)	-47.97	-45.24	24.28	2.26(6)	-68.9(7)	0.9665	0.8117	0.1548	0.06	0.01
	-46.44	-43.87	23.04	2.34(8)	-67.3(7)	0.9683	0.8000	0.1683	0.06	0.005
C(16)–O(3)	-14.32	-13.65	14.11	1.87(2)	-13.9(6)	1.4389	0.8588	0.5800	0.05	0.01
	-13.64	-12.59	14.89	1.83(2)	-11.3(1)	1.4301	0.8364	0.5937	0.08	0.04
O(3)–H(3A)	-35.31	-34.33	40.97	2.34(7)	-28.7(5)	0.9694	0.7599	0.2095	0.03	0.01
	-41.18	-39.53	34.28	2.22(7)	-46.4(6)	0.9680	0.7983	0.1698	0.04	0.02
C(13)–C(18)	-11.30	-10.73	10.44	1.71(1)	-11.6(1)	1.5369	0.7892	0.7477	0.05	0.01
C(18)–H(18A)	-16.71	-15.95	15.99	1.89(5)	-16.7(2)	1.0629	0.7085	0.3544	0.05	0.004
C(18)–H(18B)	-16.28	-15.68	13.80	1.88(5)	-18.2(2)	1.0549	0.6779	0.3771	0.04	0.01
C(18)–H(18C)	-16.05	-14.81	15.84	1.85(5)	-15.0(1)	1.0577	0.6869	0.3708	0.08	0.015

[a] λ_1, λ_2 and λ_3 are the eigenvalues of Hessian matix. $\rho(r_c)$ is the electron density; $\nabla^2\rho(r_c)$ is the Laplacian at the CP; d_1 and d_2 are the distances from the critical point; R_{ij} is the sum of d_1 & d_2; ε is the bond ellipticity. Δd is the deviation of CP from the internuclear axis

Table 5. Topological Characteristics of the electron density at the hydrogen bondcritical points[a]

bond	$\rho(\mathbf{r}_c)$ (eÅ^{-3})	$\nabla^2\rho(\mathbf{r}_c)$ (eÅ^{-5})	R_{ij} (Å)	d_1 (Å)	d_2 (Å)
m1					
O(1)–H(1A)···O(3)[a]	0.23(5)	5.07(7)	1.6869	1.1526	0.5343
O(2)–H(2A)···O(1)[b]	0.11(2)	3.00(1)	1.9287	1.2551	0.6737
O(3)–H(3A)···O(1')[c]	0.20(3)	3.00(2)	1.9328	1.2381	0.6947
m2					
O(1')–H(1'A)···O(3')[d]	0.24(5)	5.02(5)	1.6863	1.1299	0.5664
O(2')–H(2'A)···O(1')[e]	0.05(2)	2.31(1)	2.0748	1.3544	0.7204
O(2')–H(2'A)···O(2)[f]	0.20(3)	3.41(2)	1.8682	1.2186	0.6496

[a] Symmetry codes: (a) -x+2, y-½, -z+1; (b) -x+1, y+½, -z+1; (c) x, y, z-1 ; (d) -x+1, y+½, -z+2; (e) -x+2, y-½, -z+2; (f) -x+1, y-½, -z+1

Table 6a. Net atomic charges (e) for the molecule 1 (first row) and 2 (second row)

Atom	charge	Atom	charge
C(1)	-0.21(3)	H(6A)	0.20(2)
C(2)	-0.06(3)	H(6B)	0.12(2)
C(3)	0.16(3)	H(7A)	0.20(2)
C(4)	-0.06(3)	H(7B)	0.24(2)
C(5)	0.00	H(8)	0.16(2)
C(10)	-0.04(2)	H(9)	0.20(2)
C(6)	-0.36(3)	H(11A)	0.20(2)
C(7)	-0.48(3)	H(11B)	0.22(2)
C(8)	-0.12(3)	H(12A)	0.08(2)
C(9)	-0.29(3)	H(12B)	0.26(2)
C(11)	-0.31(3)	H(14)	0.17(2)
C(12)	-0.47(3)	H(15A)	0.30(2)
C(13)	0.00	H(15B)	0.21(2)
C(14)	-0.07(3)	H(16)	0.21(2)
C(15)	-0.24(3)	H(17)	0.16(2)
C(16)	0.05(3)	H(18A)	0.20(2)
C(17)	-0.08(3)	H(18B)	0.27(2)
C(18)	-0.61(3)	H(18C)	0.19(2)
O(1)	-0.63(3)	H(1A)	0.43(3)
	-0.79(3)		0.35(3)
O(2)	-0.86(3)	H(2A)	0.48(2)
	-0.87(3)		0.46(2)
O(3)	-0.84(3)	H(3A)	0.25(2)
	-0.77(3)		0.46(2)
H(1)	0.16(2)		
H(2)	0.29(2)		
H(4)	0.31(2)		

Table 6b. Group charge(e) calculation for the molecule 1 (first row) and 2 (second row)

Atoms	charge(e)
C(3), O(1), H(1A)	-0.04
	-0.20
C(17), H(17), O(2A), H(2A)	-0.30
	-0.33
C(16), H(16), O(3A), H(3A)	-0.33
	-0.05
C(1), H(1), C(10)	-0.05
C(2), H(2)	0.23
C(4), H(4)	0.28
C(6), C(7), H(6A), H(6B)	-0.08
H(7A), H(7B)	
C(11), C(12), H(11A), H(11B)	-0.02
H(12A), H(12B)	
C(14), H(14), C(15), H(15A), H(15B)	0.37

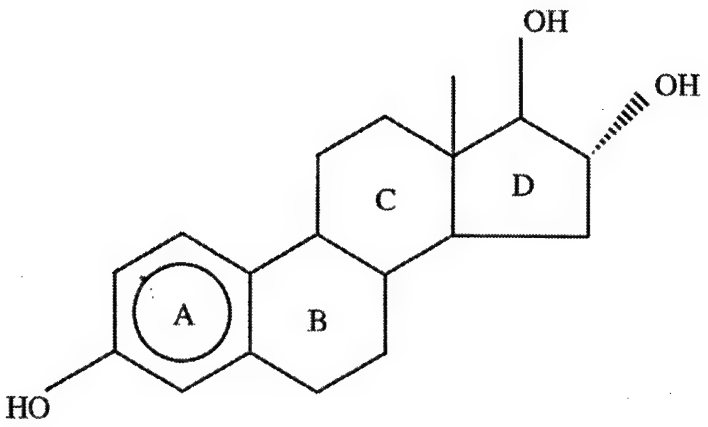


Figure 1. Estriol

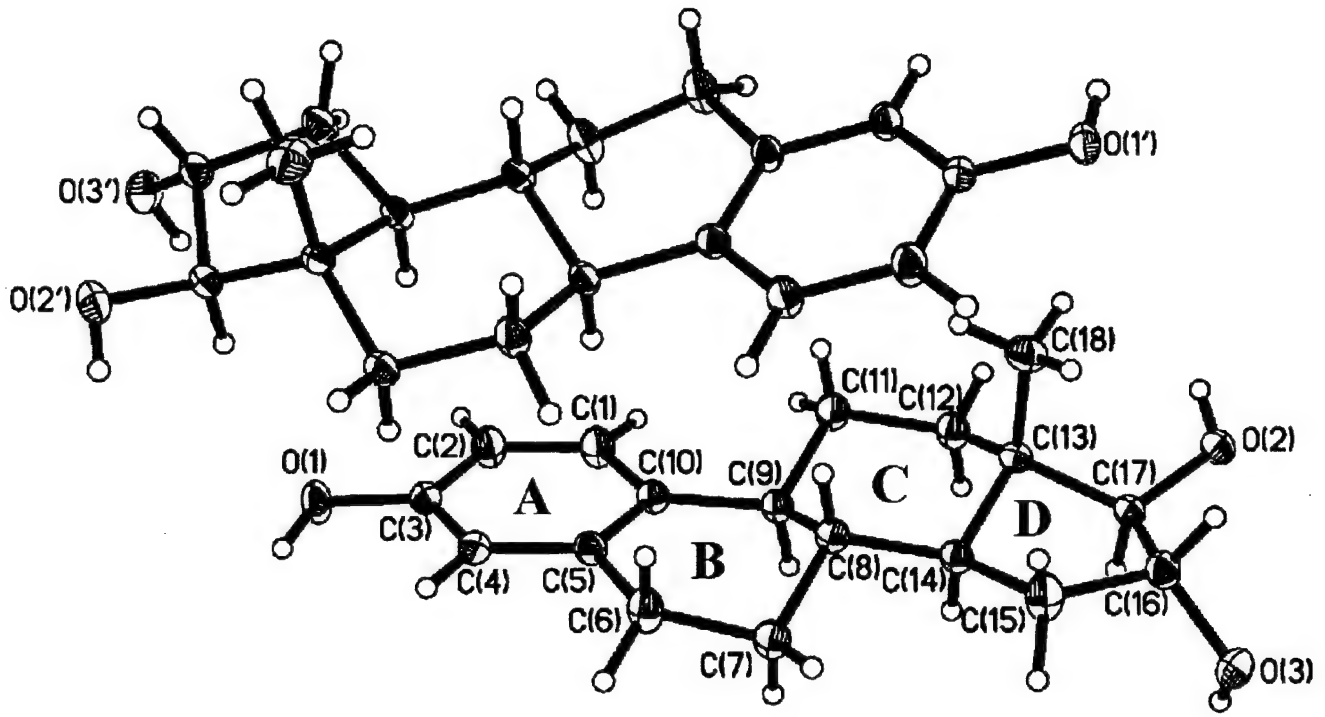


Figure 2. ORTEP view of two molecules in the asymmetric unit showing 75% probability ellipsoids of the atoms and atomic labeling.

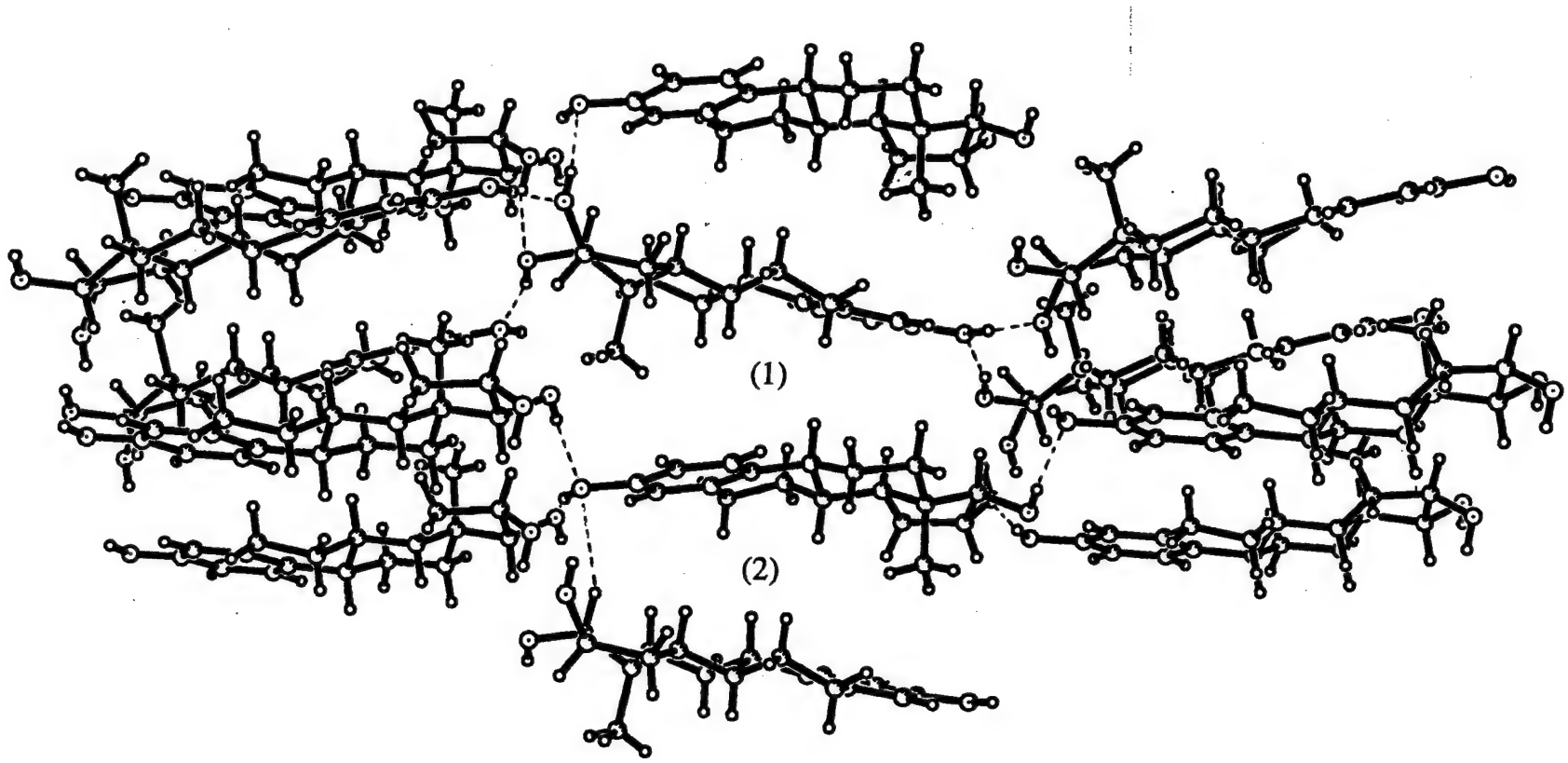


Figure 3. Intermolecular hydrogen bonding view of molecules 1 and 2.

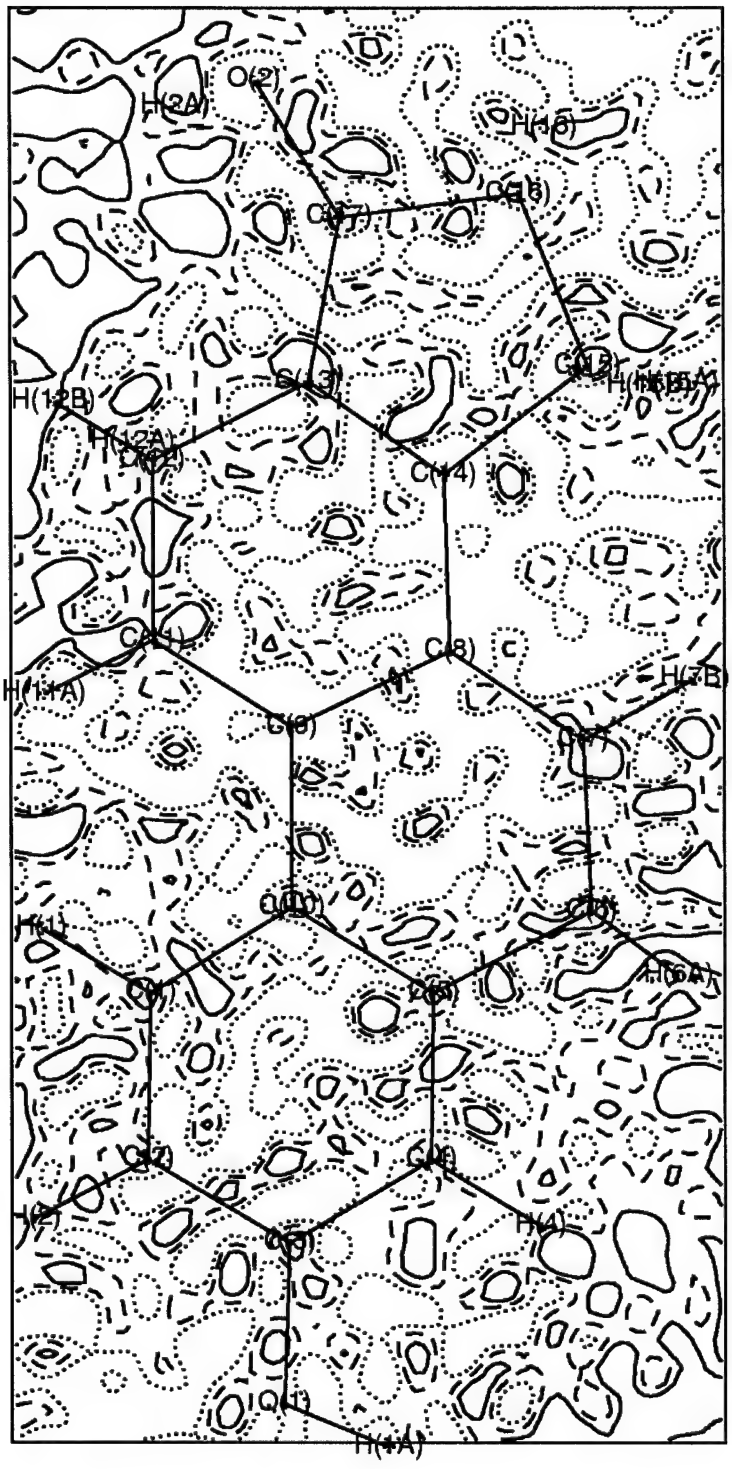


Figure 4a. Residual density maps for molecule 1 in the plane of C(1), C(5) and C(16) . Contour interval 0.05 eÅ^{-3}. Positive, negative and zero contours are drawn as solid, dotted and broken lines respectively.

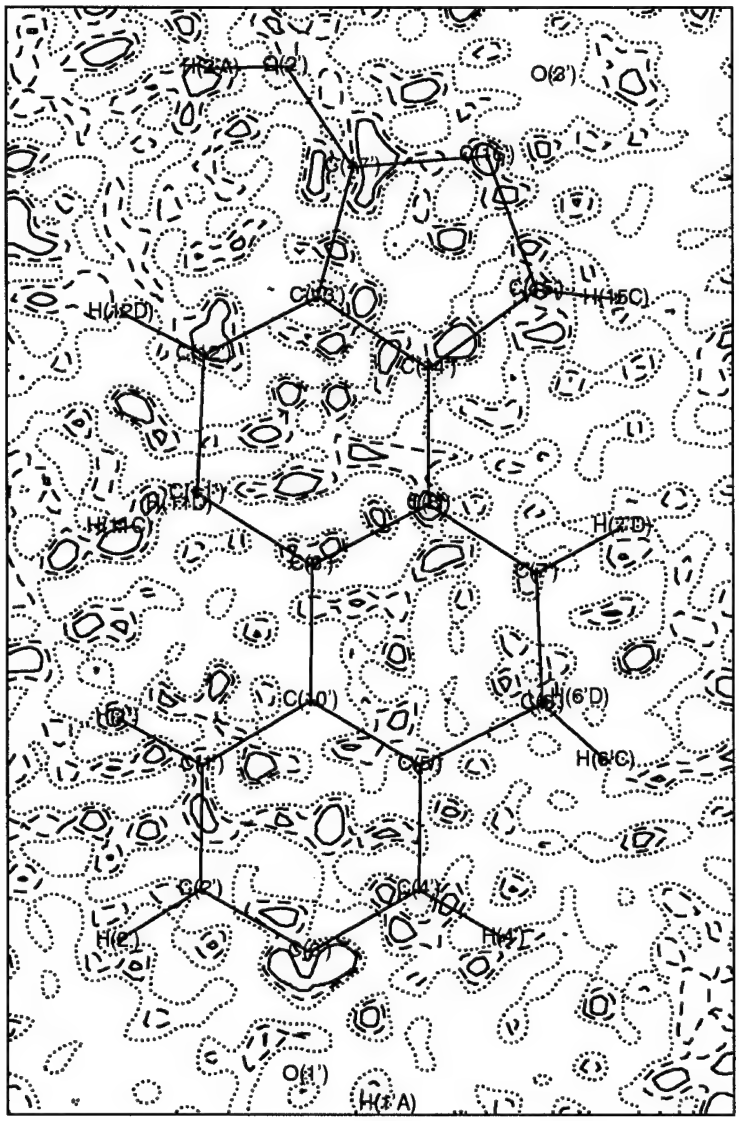


Figure 4b. Residual density maps for molecule 2 in the C(1') C(5') C(16') plane. Contour interval 0.05 eÅ^{-3}. Positive, negative and zero contours are drawn as solid, dotted and broken lines respectively.

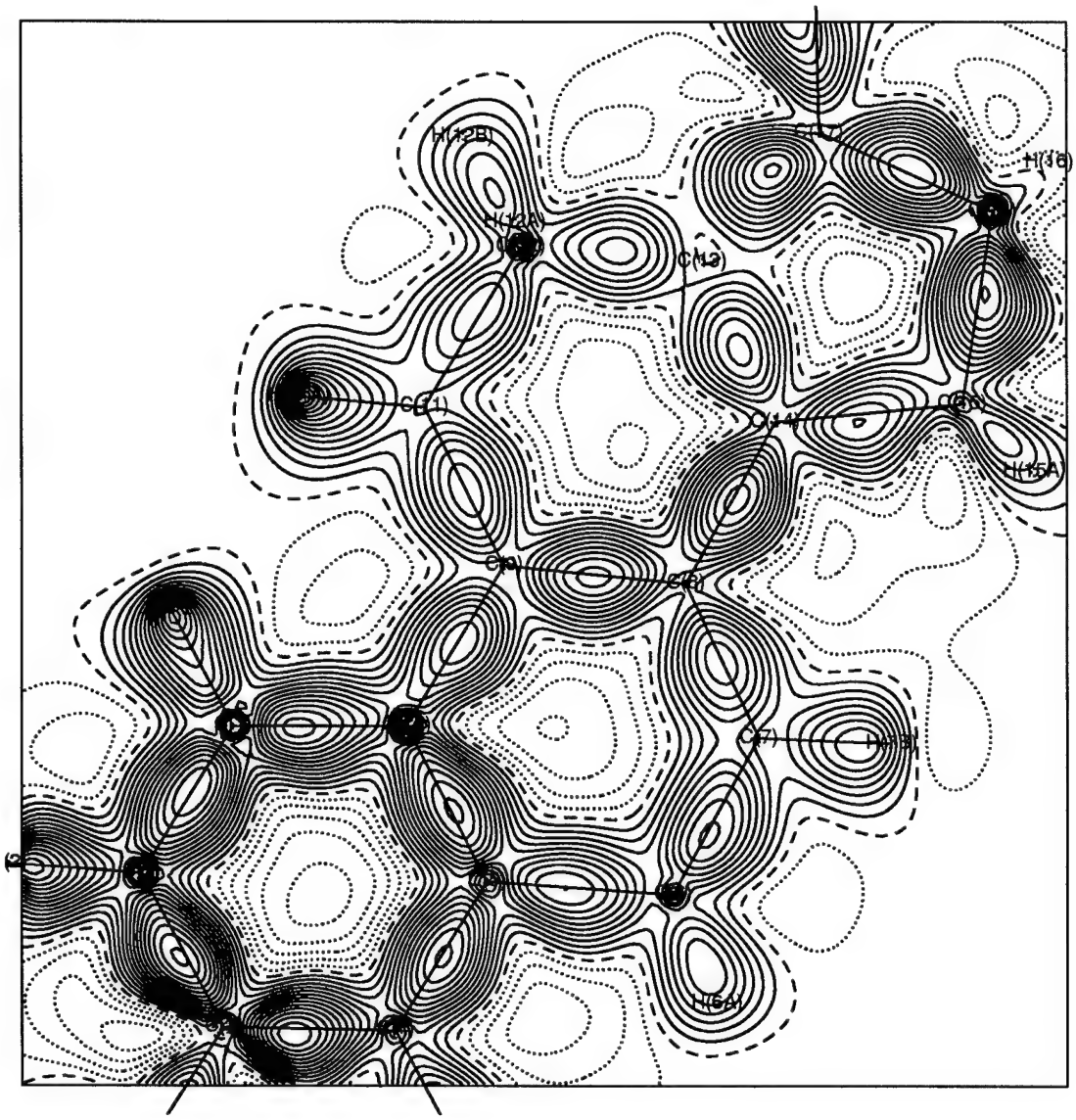


Figure 5. Static deformation density map of molecule 1. Contour intervals 0.05 eÅ^{-3}. Positive solid line, negative dotted line and zero contour broken line.

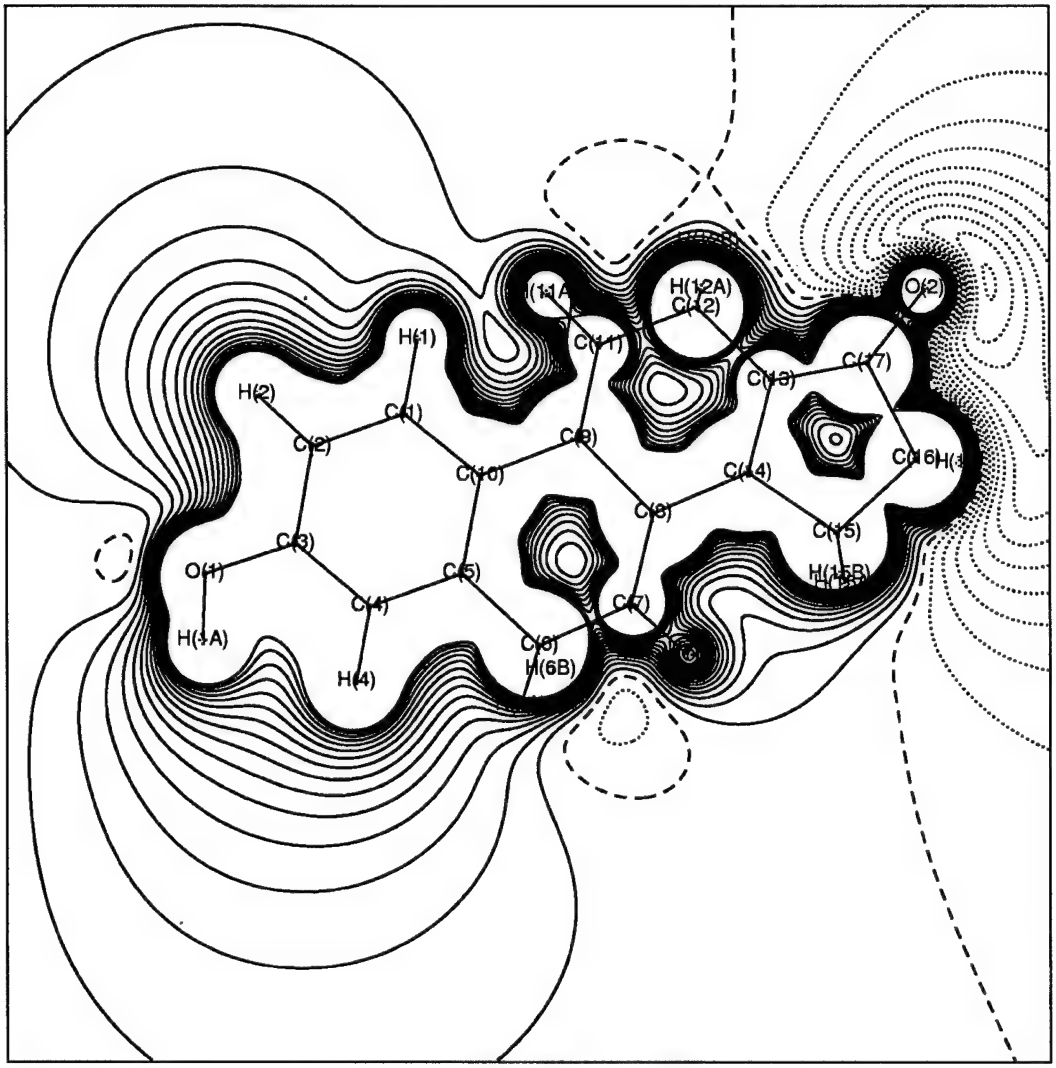


Figure 6a. Electrostatic potential contour map of molecule 1 in the plane of O(1), C(5) and C(16). Contour interval 0.05 $e\text{Å}^{-3}$; Positive contour is solid line, negative contour is dotted line and zero contour is broken line.

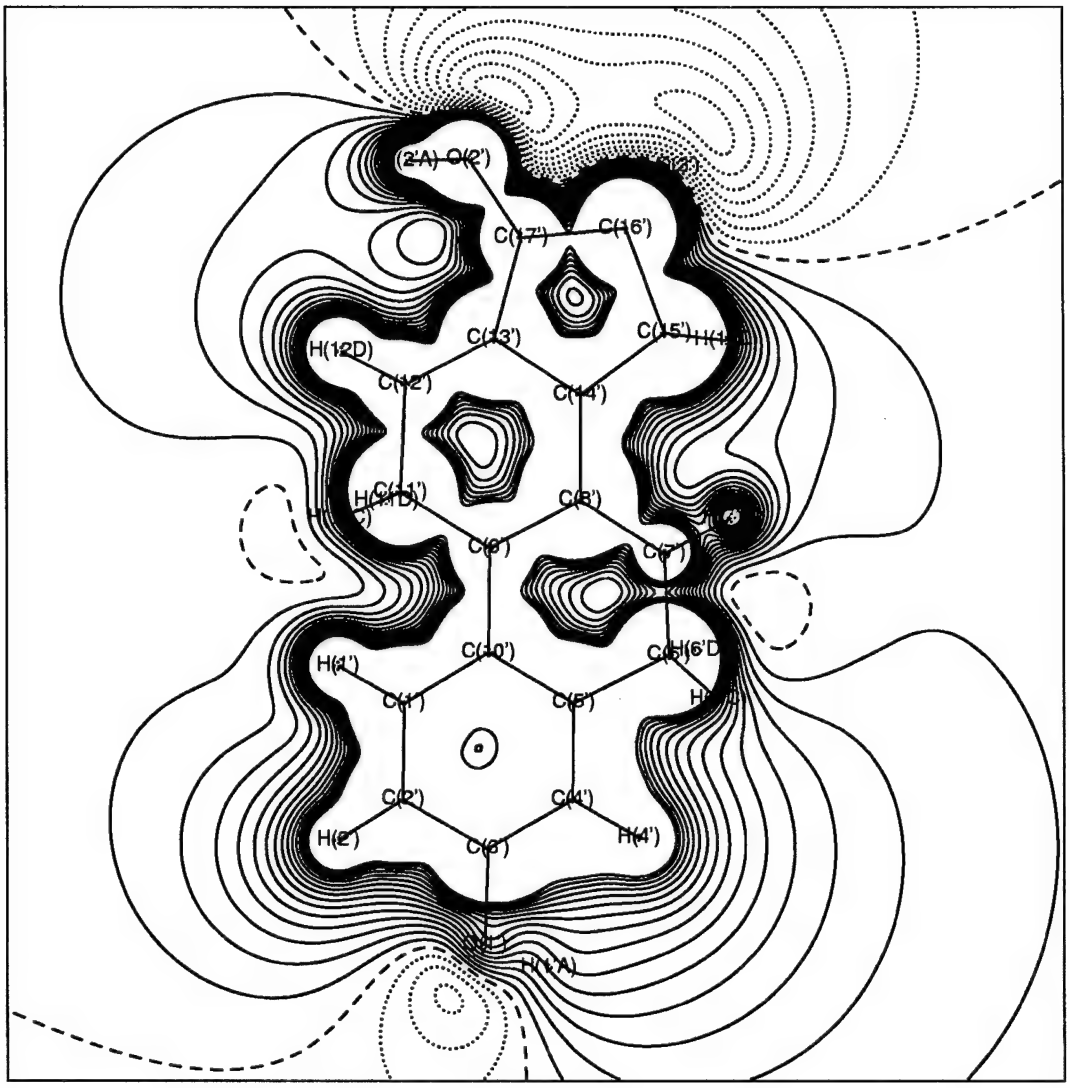


Figure 6b. Electrostatic potential contour map of molecule 2 in the plane of C(1'), C(5') and C(16'). Contour interval 0.05 eÅ^{-3}; Positive contour is solid line, negative contour is dotted line and zero contour is broken line.

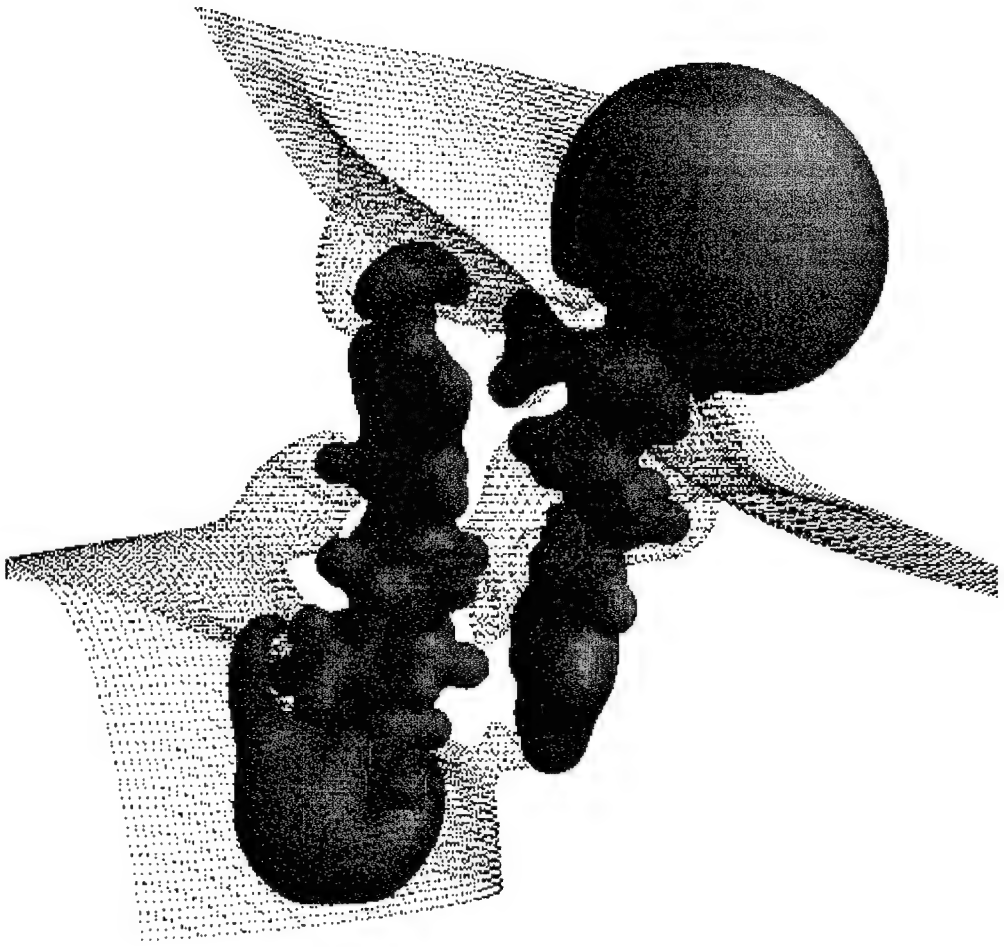


Figure 7. Isosurface representation of electrostatic potential of molecule 1 (right) and 2 (left). Surfaces are drawn at constant positive and negative potentials of 0.5 /e/Å (red) and –0.1 e/Å (green). Grey dots represent zero surface.

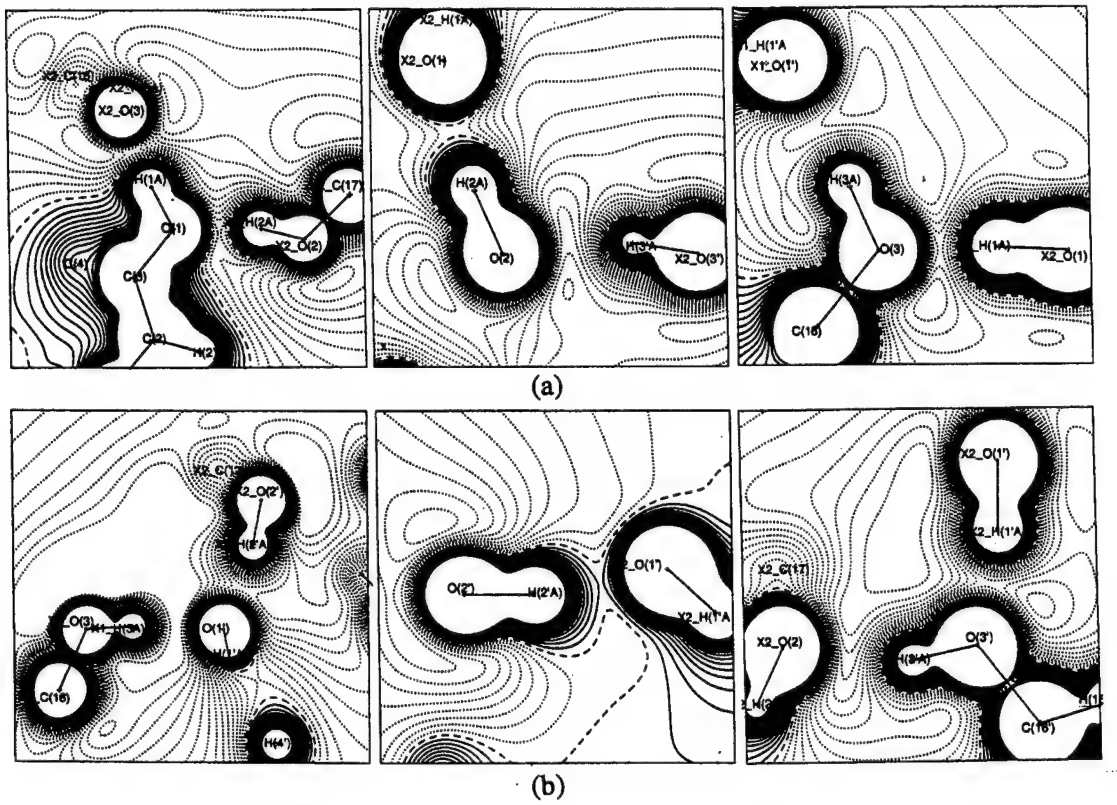


Figure 8. The electrostatic potential in the hydrogen bonding environment of oxygen atoms of (a) molecule 1 and (b) molecule 2. Contour interval 0.05 eÅ^{-3}; Positive solid lines, negative dotted lines and zero contours are broken lines.

Supplementary Tables

Table S1. Fractional coordinates, equivalent displacement parameters (Å^2) after multipole refinement[a]

Atom	x	y	z	U_{eq}
Molecule 1				
O(1)	0.51768(10)	0.85352(11)	0.52120(11)	0.018
O(2)	0.79921(9)	1.32161(11)	0.40944(9)	0.015
O(3)	1.19065(9)	1.28089(11)	0.40369(9)	0.015
C(1)	0.45782(8)	1.00729(11)	0.42503(8)	0.014
C(2)	0.41442(8)	0.94969(11)	0.44370(8)	0.016
C(3)	0.56255(8)	0.91059(11)	0.51231(7)	0.012
C(4)	0.75074(7)	0.93004(11)	0.56560(6)	0.011
C(5)	0.79388(7)	0.98789(11)	0.54672(6)	0.010
C(6)	1.00170(8)	1.00579(11)	0.60531(7)	0.013
C(7)	1.03656(7)	1.06192(11)	0.53178(7)	0.013
C(8)	0.89489(7)	1.10844(11)	0.53900(6)	0.010
C(9)	0.69131(7)	1.08931(11)	0.43663(6)	0.010
C(10)	0.64664(7)	1.02772(11)	0.47414(6)	0.010
C(11)	0.54265(8)	1.13507(11)	0.43759(7)	0.013
C(12)	0.58776(7)	1.19493(11)	0.38487(7)	0.012
C(13)	0.78969(7)	1.21485(11)	0.48383(6)	0.010
C(14)	0.93243(7)	1.16700(11)	0.47888(6)	0.010
C(15)	1.12818(8)	1.19665(11)	0.55149(8)	0.015
C(16)	1.08802(7)	1.26090(11)	0.49990(7)	0.012
C(17)	0.87053(7)	1.26401(11)	0.41297(6)	0.010
C(18)	0.80161(10)	1.23048(11)	0.65010(7)	0.017
H(1A)	0.63209	0.82990	0.55330	0.034
H(2A)	0.69428	1.32373	0.44686	0.012
H(3A)	1.13395	1.27295	0.29273	0.025
H(1)	0.34450	1.03712	0.36414	0.029
H(2)	0.26604	0.93672	0.39812	0.044
H(4)	0.86510	0.89941	0.61941	0.021
H(6A)	1.09283	0.97171	0.58700	0.037
H(6B)	1.04093	1.01387	0.73024	0.020
H(7A)	1.01476	1.05396	0.40896	0.015
H(7B)	1.18207	1.07730	0.59177	0.021
H(8)	0.89840	1.11151	0.65964	0.017
H(9)	0.68554	1.08694	0.31532	0.016
H(11A)	0.40304	1.12061	0.35796	0.024
H(11B)	0.53292	1.13757	0.55336	0.020
H(12A)	0.57626	1.19302	0.26278	0.018
H(12B)	0.48167	1.22649	0.38902	0.019
H(14)	0.90581	1.15747	0.35520	0.014
H(15A)	1.23477	1.17769	0.51002	0.022
H(15B)	1.18913	1.19417	0.67908	0.024
H(16)	1.12808	1.29047	0.60016	0.025
H(17)	0.84636	1.25096	0.29187	0.011
H(18A)	0.76328	1.19583	0.70939	0.033
H(18B)	0.70167	1.26365	0.64136	0.026
H(18C)	0.94099	1.24472	0.71651	0.025
Molecule 2				
O(1')	0.98786(9)	1.26560(11)	1.07236(8)	0.013
O(2')	0.74949(10)	0.79556(11)	1.08083(9)	0.016

O(3')	0.31379(9)	0.81942(11)	0.90942(8)	0.015
C(1')	1.04605(7)	1.10997(11)	1.03189(7)	0.013
C(2')	1.08893(7)	1.16877(11)	1.05868(7)	0.013
C(3')	0.94251(7)	1.20768(11)	1.04700(6)	0.010
C(4')	0.75670(7)	1.18771(11)	1.01090(6)	0.010
C(5')	0.71459(7)	1.12874(11)	0.98527(6)	0.009
C(6')	0.51022(7)	1.11043(11)	0.95313(8)	0.013
C(7')	0.47065(7)	1.04728(11)	0.90310(7)	0.012
C(8')	0.63563(7)	1.00865(11)	0.99989(6)	0.009
C(9')	0.81329(7)	1.02453(11)	0.96109(6)	0.009
C(10')	0.86001(7)	1.08860(11)	0.99460(6)	0.010
C(11')	0.98227(7)	0.98340(11)	1.03926(7)	0.012
C(12')	0.92732(7)	0.91892(11)	1.00723(7)	0.012
C(13')	0.75705(7)	0.90425(11)	1.05525(6)	0.009
C(14')	0.59061(7)	0.94487(11)	0.96631(6)	0.009
C(15')	0.41989(8)	0.91948(11)	0.99963(8)	0.014
C(16')	0.46119(8)	0.85355(11)	1.01718(7)	0.012
C(17')	0.65666(8)	0.84557(11)	0.99892(6)	0.011
C(18')	0.81622(9)	0.90814(11)	1.23340(6)	0.015
H(1'A)	0.87426	1.28653	1.06698	0.027
H(2'A)	0.84956	0.78829	1.03968	0.022
H(3'A)	0.28464	0.83420	0.80471	0.020
H(1')	1.15901	1.07987	1.03660	0.026
H(2')	1.23032	1.18590	1.08056	0.026
H(4')	0.64298	1.21784	1.00111	0.021
H(6'A)	0.41147	1.14015	0.87102	0.027
H(6'B)	0.48205	1.11487	1.06167	0.014
H(7'A)	0.44868	1.04194	0.77938	0.024
H(7'B)	0.33470	1.03427	0.91168	0.021
H(8')	0.66573	1.01546	1.12513	0.012
H(9')	0.77340	1.01922	0.83423	0.011
H(11'A)	1.09205	0.99035	0.98873	0.020
H(11'B)	1.04447	0.99134	1.16493	0.017
H(12'A)	0.89389	0.91066	0.88280	0.018
H(12'B)	1.05438	0.89402	1.07392	0.029
H(14')	0.56308	0.93793	0.84142	0.012
H(15'A)	0.28167	0.92827	0.90891	0.023
H(15'A)	0.40421	0.93935	1.10220	0.016
H(16')	0.48007	0.83935	1.13620	0.015
H(17')	0.62869	0.84147	0.87314	0.014
H(18'A)	0.86807	0.94995	1.27305	0.017
H(18'B)	0.92207	0.87636	1.28493	0.022
H(18'C)	0.70244	0.89942	1.27329	0.032

[a] $U_{eq} = \frac{1}{2} (\Sigma_i \Sigma_j U_{ij} a_i^* a_j^* \mathbf{a}_i \cdot \mathbf{a}_j)$

Table S2. Anisotropic thermal parameters of non-Hydrogen atoms ($Å^2$) and estimated standard deviations.

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Molecule 1						
O(1)	0.0125(2)	0.0088(2)	0.0312(3)	-0.0001(2)	0.0108(2)	0.0023(2)
O(2)	0.0146(2)	0.0087(2)	0.0217(3)	0.0028(1)	0.0102(2)	0.0011(2)
O(3)	0.0113(2)	0.0137(2)	0.0187(2)	-0.0034(2)	0.0066(2)	-0.0017(2)
C(1)	0.0083(2)	0.0111(2)	0.0211(2)	0.0005(1)	0.0039(2)	0.0019(2)
C(2)	0.0094(2)	0.0109(2)	0.0250(3)	-0.0003(1)	0.0062(2)	0.0016(2)
C(3)	0.0109(2)	0.0089(1)	0.0164(2)	0.0002(1)	0.0071(1)	0.0008(1)
C(4)	0.0103(2)	0.0096(1)	0.0120(2)	0.0005(1)	0.0048(1)	0.0009(1)
C(5)	0.0087(1)	0.0086(1)	0.0102(2)	0.0005(1)	0.0029(1)	0.0007(1)
C(6)	0.0085(2)	0.0104(2)	0.0167(2)	0.0010(1)	0.0015(1)	0.0032(1)
C(7)	0.0083(2)	0.0104(2)	0.0170(2)	0.0018(1)	0.0041(1)	0.0024(1)
C(8)	0.0080(1)	0.0089(1)	0.0104(2)	0.0008(1)	0.0024(1)	0.0010(1)
C(9)	0.0076(1)	0.0087(1)	0.0108(2)	0.0011(1)	0.0022(1)	0.0008(1)
C(10)	0.0080(1)	0.0090(1)	0.0112(2)	0.0004(1)	0.0026(1)	0.0007(1)
C(11)	0.0085(2)	0.0099(2)	0.0194(2)	0.0014(1)	0.0054(1)	0.0017(1)
C(12)	0.0086(2)	0.0094(2)	0.0163(2)	0.0014(1)	0.0034(1)	0.0016(1)
C(13)	0.0092(1)	0.0085(1)	0.0106(2)	0.0005(1)	0.0042(1)	-0.0005(1)
C(14)	0.0078(1)	0.0086(1)	0.0111(2)	0.0010(1)	0.0029(1)	0.0007(1)
C(15)	0.0081(2)	0.0115(2)	0.0214(2)	0.0006(1)	0.0020(2)	0.0023(2)
C(16)	0.0097(2)	0.0096(2)	0.0147(2)	-0.0005(1)	0.0041(1)	-0.0009(1)
C(17)	0.0097(2)	0.0080(1)	0.0123(2)	0.0010(1)	0.0048(1)	0.0001(1)
C(18)	0.0216(2)	0.0145(2)	0.0123(2)	-0.0001(2)	0.0089(2)	-0.0018(2)
Molecule 2						
O(1')	0.0118(2)	0.0071(1)	0.0182(2)	-0.0011(1)	0.0073(2)	-0.0007(1)
O(2')	0.0171(2)	0.0093(2)	0.0201(3)	0.0029(2)	0.0096(2)	0.0024(2)
O(3')	0.0145(2)	0.0111(2)	0.0167(2)	-0.0051(2)	0.0065(2)	-0.0028(2)
C(1')	0.0082(1)	0.0087(1)	0.0217(2)	0.0000(1)	0.0066(1)	-0.0009(2)
C(2')	0.0092(2)	0.0083(2)	0.0211(2)	-0.0007(1)	0.0067(2	-0.0005(1)
C(3')	0.0097(1)	0.0073(1)	0.0128(2)	-0.0004(1)	0.0053(1)	-0.0003(1)
C(4')	0.0089(1)	0.0069(1)	0.0134(2)	0.0002(1)	0.0041(1)	0.0002(1)
C(5')	0.0074(1)	0.0070(1)	0.0125(2)	0.0004(1)	0.0032(1)	0.0001(1)
C(6')	0.0071(1)	0.0089(1)	0.0212(2)	0.0007(1)	0.0034(1)	-0.0006(1)
C(7')	0.0075(1)	0.0087(2)	0.0175(2)	0.0003(1)	0.0008(1)	-0.0020(1)
C(8')	0.0072(1)	0.0073(1)	0.0115(2)	-0.0001(1)	0.0034(1)	-0.0016(1)
C(9')	0.0084(1)	0.0067(1)	0.0114(2)	0.0003(1)	0.0041(1)	-0.0006(1)
C(10')	0.0078(1)	0.0076(1)	0.0123(2)	0.0004(1)	0.0040(1)	0.0000(1)
C(11')	0.0080(1)	0.0085(1)	0.0175(2)	0.0008(1)	0.0047(1)	0.0005(1)
C(12')	0.0103(2)	0.0084(1)	0.0157(2)	0.0014(1)	0.0069(1)	0.0002(1)
C(13')	0.0090(1)	0.0083(1)	0.0089(1)	0.0000(1)	0.0040(1)	-0.0007(1)
C(14')	0.0080(1)	0.0073(1)	0.0113(2)	-0.0003(1)	0.0032(1)	-0.0020(1)
C(15')	0.0099(2)	0.0091(2)	0.0220(2)	-0.0015(1)	0.0078(2)	-0.0035(2)
C(16')	0.0119(2)	0.0080(1)	0.0144(2)	-0.0017(1)	0.0066(1)	-0.0019(1)
C(17')	0.0117(2)	0.0076(1)	0.0121(2)	-0.0003(1)	0.0060(1)	-0.0013(1)
C(18')	0.0175(2)	0.0149(2)	0.0095(2)	-0.0022(2)	0.0044(2)	-0.0009(1)

The thermal parameters are listed in the form of $\exp\{-2\pi^2(U_{11}h^2a^{*2}+2U_{12}hka^*b^*+\cdots)\}$

Table S3. Bond angles (deg)

bond	m 1	m2
C(2)–C(1)–H(1)	119.7(2)	119.2(2)
C(10)–C(1)–H(1)	117.9(2)	118.7(2)
C(1)–C(2)–H(2)	118.0(2)	122.5(2)
C(3)–C(2)–H(2)	122.6(2)	118.3(2)
C(3)–C(4)–H(4)	119.2(2)	120.1(2)
C(5)–C(4)–H(4)	119.8(2)	119.2(2)
C(5)–C(6)–H(6A)	111.8(1)	110.5(2)
C(5)–C(6)–H(6B)	106.0(1)	108.0(1)
C(7)–C(6)–H(6A)	109.1(1)	112.5(2)
C(7)–C(6)–H(6B)	107.1(2)	106.4(2)
H(6A)–C(6)–H(6B)	109.6(2)	105.3(2)
C(6)–C(7)–H(7A)	109.0(2)	111.1(2)
C(6)–C(7)–H(7B)	110.6(2)	109.1(2)
C(8)–C(7)–H(7A)	108.2(1)	109.1(1)
C(8)–C(7)–H(7B)	109.6(2)	112.5(2)
H(7A)–C(7)–H(7B)	109.1(1)	104.2(1)
C(7)–C(8)–H(8)	108.8(1)	110.1(1)
C(9)–C(8)–H(8)	107.0(1)	109.6(1)
C(14)–C(8)–H(8)	111.4(2)	107.4(2)
C(8)–C(9)–H(9)	107.5(1)	106.6(1)
C(10)–C(9)–H(9)	104.4(2)	106.1(2)
C(11)–C(9)–H(9)	105.9(1)	106.9(1)
C(9)–C(11)–H(11A)	108.1(2)	109.5(2)
C(9)–C(11)–H(11B)	110.1(2)	110.9(2)
C(12)–C(11)–H(11A)	109.3(2)	104.6(2)
C(12)–C(11)–H(11B)	110.9(2)	110.3(2)
H(11A)–C(11)–H(11B)	106.5(1)	108.2(1)
C(11)–C(12)–H(12A)	109.8(2)	108.3(2)
C(11)–C(12)–H(12B)	110.1(2)	106.3(2)
C(13)–C(12)–H(12A)	108.5(1)	110.9(1)
C(13)–C(12)–H(12B)	111.1(1)	112.0(1)
H(12A)–C(12)–H(12B)	105.8(2)	108.7(2)
C(8)–C(14)–H(14)	101.9(2)	107.3(2)
C(13)–C(14)–H(14)	107.4(1)	106.1(1)
C(15)–C(14)–H(14)	109.1(1)	107.0(1)
C(14)–C(15)–H(15A)	112.1(1)	114.3(1)
C(14)–C(15)–H(15B)	114.1(1)	111.5(1)
C(16)–C(15)–H(15A)	111.3(2)	111.2(2)
C(16)–C(15)–H(15B)	109.7(2)	113.8(2)
H(15A)–C(15)–H(15B)	105.8(1)	102.2(2)
O(3)–C(16)–H(16)	105.5(1)	108.4(2)

C(15)–C(16)–H(16)	120.0(2)	110.2(2)
C(17)–C(16)–H(16)	109.0(1)	106.4(1)
O(2)–C(17)–H(17)	107.8(2)	111.0(2)
C(13)–C(17)–H(17)	106.1(2)	108.2(2)
C(16)–C(17)–H(17)	105.6(1)	106.9(1)
C(13)–C(18)–H(18A)	113.5(1)	110.5(1)
C(13)–C(18)–H(18B)	107.9(1)	108.6(1)
C(13)–C(18)–H(18C)	109.8(1)	113.1(1)
H(18A)–C(18)–H(18B)	105.6(1)	110.7(1)
H(18A)–C(18)–H(18C)	109.4(2)	107.3(2)
H(18B)–C(18)–H(18C)	110.4(3)	106.4(2)

Table S4. Multipole population coefficients for the atoms of molecule 1 (first row) and 2 (second row)[a].

Atom	M1	D0	D1+	D1-	Q0	Q1+	Q1-	Q2+	Q2-
O(1)	6.51(4)	-0.04(2)	-0.09(2)	-0.01(2)	0.04(2)	-0.02(2)	-0.04(2)	-0.06(2)	- 0.01(2)
	6.68(4)	-0.05(2)	-0.06(2)	-0.04(2)	0.04(2)	0.01(2)	0.01(2)	-0.05(2)	0.00
O(2)	6.71(4)	0.08(2)	-0.03(2)	-0.05(2)	0.07(2)	0.00	-0.08(2)	-0.07(2)	-0.02(2)
	6.69(4)	0.03(2)	-0.06(2)	-0.06(2)	0.08(2)	0.05(2)	0.04(2)	-0.05(2)	0.02(2)
O(3)	6.82(4)	-0.03(2)	-0.06(2)	-0.03(2)	-0.02(2)	0.00	0.00	-0.06(2)	-0.03(2)
	6.74(4)	0.01(2)	-0.09(2)	-0.03(2)	0.04(2)	0.05(2)	-0.08(2)	-0.08(2)	-0.07(2)
C(1)	4.21(6)	-0.11(3)	0.00	0.05(4)	-0.25(3)	-0.03(3)	0.05(3)	0.00	-0.02(3)
C(2)	3.80(6)	0.03(3)	-0.05(4)	0.00	-0.24(3)	0.00	0.04(2)	0.05(3)	-0.08(3)
C(3)	3.87(6)	0.00	0.23(4)	0.13(4)	-0.33(2)	0.00	-0.06(2)	0.00	-0.07(3)
C(4)	3.65(6)	0.16(3)	0.14(4)	0.00	-0.21(2)	-0.03(2)	0.00	0.00	0.01(3)
C(5)	3.88(6)	0.00	0.09(4)	-0.02(4)	-0.31(3)	-0.03(3)	-0.01(3)	-0.01(3)	-0.01(3)
C(6)	4.25(6)	0.09(3)	-0.10(3)	-0.15(3)	0.00	-0.10(2)	0.00	0.03(2)	0.04(2)
C(7)	4.48(6)	0.00	-0.12(3)	0.01(3)	0.00	0.05(2)	-0.04(2)	0.07(2)	-0.05(2)
C(8)	4.07(6)	0.13(3)	-0.05(3)	-0.12(3)	0.06(2)	-0.09(2)	-0.08(2)	0.01(2)	0.04(2)
C(9)	4.11(6)	0.01(2)	0.12(3)	0.02(2)	0.00	0.00	0.01(2)	-0.01(2)	-0.05(2)
C(10)	3.69(6)	-0.04(3)	0.07(4)	0.00	-0.13(3)	0.01(3)	0.05(2)	-0.04(3)	-0.08(3)
C(11)	4.25(5)	-0.08(3)	-0.08(3)	0.02(3)	0.00	-0.03(2)	-0.06(2)	0.00	0.04(2)
C(12)	4.29(6)	-0.14(3)	-0.12(3)	0.08(3)	0.04(2)	0.05(2)	-0.03(2)	0.06(2)	-0.05(2)
C(13)	3.86(6)	0.05(3)	0.04(3)	-0.03(3)	-0.04(2)	-0.15(2)	0.00	0.05(2)	0.04(2)
C(14)	4.06(6)	-0.10(3)	-0.13(3)	0.08(3)	0.00	0.06(2)	-0.08(2)	-0.08(2)	0.06(2)
C(15)	4.08(5)	0.00	-0.12(3)	-0.07(3)	-0.04(2)	-0.03(2)	-0.17(3)	0.00	0.09(2)
C(16)	4.23(5)	0.09(3)	0.07(3)	-0.10(3)	0.05(2)	-0.11(2)	-0.03(2)	0.00	0.13(2)
C(17)	4.23(5)	-0.16(3)	-0.06(3)	0.09	0.03(2)	0.05(2)	-0.03(2)	0.00	-0.13(2)
C(18)	4.35(6)	-0.14(3)	0.10(3)	0.03(3)	0.05(2)	-0.03(3)	0.02(3)	-0.06(2)	-0.03(3)
H(1A)	0.64(4)	0.13(3)							
	0.73(3)	0.13(3)							
H(2A)	0.69(3)	0.21(2)							
	0.73(3)	0.25(3)							
H(3A)	0.94(3)	0.10(2)							
	0.76(3)	0.12 (2)							
H(1)	1.00(4)	0.10(2)							
H(2)	0.80(3)	0.25(2)							
H(4)	0.79(3)	0.21(2)							
H(6A)	1.00(4)	0.22(2)							
H(6B)	0.94(3)	0.01(2)							
H(7A)	0.85(3)	0.11(2)							
H(7B)	0.92(3)	0.13(3)							
H(8)	0.81(3)	0.03(2)							
H(9)	0.89(3)	0.11(2)							
H(11A)	0.96(3)	0.07(2)							
H(11B)	0.90(3)	0.13(2)							
H(12A)	0.88(3)	0.02(2)							
H(12B)	0.91(3)	0.20(2)							
H(14)	0.79(3)	0.05(2)							
H(15A)	0.79(3)	0.18(2)							
H(15B)	0.76(3)	0.03(2)							
H(16)	0.74(3)	0.14(2)							
H(17)	0.75(30	0.05(2)							
H(18A)	0.94(4)	0.10(2)							
H(18B)	0.90(4)	0.19(2)							
H(18C)	1.00(4)	0.10(2)							

All the ring (A, B, C, D) atoms of the molecule 1 has been constrained equal to molecule 2.

Atom	O0	O1+	O1-	O2+	O2-	O3+	O3-	H0	H1+	H1-	H2+	H2-	H3+	H3-	H4+	H4-
O(1)	-0.05(2)	0.03(2)	-0.03(2)	0.03(2)	-0.05(2)	0.05(2)	-0.02(2)	0.03(3)	0.01(2)	0.03(2)	0.06(2)	0.04(2)	-0.02(2)	0.02(2)	0.04(2)	0.06(2)
	-0.02(2)	-0.03(2)	-0.03(2)	0.00	-0.01(2)	0.11(2)	-0.06(2)	0.06 (2)	0.01(2)	-0.04(2)	-0.04(2)	0.03(2)	0.00	0.03(2)	0.04(2)	0.00
O(2)'	-0.02(2)	0.00	0.00	0.03(2)	0.01(2)	0.122)	0.02(2)	0.00	-0.03(2)	-0.01(2)	-0.03(2)	-0.01(2)	-0.02(2)	0.06(2)	-0.03(2)	0.08(2)
	-0.04(2)	-0.01(2)	-0.02(2)	0.01(2)	0.04(2)	0.08(2)	-0.04(2)	-0.05(2)	0.00	-0.06(2)	0.06(2)	0.02(2)	-0.07(2)	-0.05(2)	0.00	0.01(2)
O(3)	0.03(2)	-0.01(2)	0.06(2)	-0.01(2)	-0.02(2)	0.06(2)	-0.08(2)	0.01(2)	0.07(2)	0.04(2)	0.01(2)	0.06(2)	-0.03(2)	0.01(2)	0.04(2)	-0.03(2)
	0.05(2)	-0.04(2)	0.01(2)	0.03(2)	0.01(2)	0.09(2)	-0.05(2)	-0.05(2)	-0.06(2)	0.03(2)	0.01(2)	0.02(2)	-0.06(2)	0.07(2)	-0.02(2)	0.04(2)
C(1)	0.03(3)	0.01(3)	-0.02(3)	0.03(3)	0.00	0.51(4)	0.04(3)	0.05(3)	0.00	0.03(3)	-0.03(3)	0.02(4)	0.00	0.00	0.08(3)	0.07(4)
C(2)	-0.01(3)	0.00	0.06(3)	0.03(3)	0.00	0.46(4)	-0.10(4)	0.06(4)	0.06(3)	0.00	0.03(4)	0.00	0.11(3)	0.03(3)	0.01(4)	-0.22(3)
C(3)	0.00	0.00	0.05(3)	0.00	0.00	0.58(4)	-0.07(3)	0.12(3)	0.00	0.00	0.02(3)	0.04(3)	-0.06(4)	0.06(4)	-0.01(4)	-0.14(4)
C(4)	0.07(3)	0.00	0.00	0.05(3)	-0.06(3)	0.41(4)	-0.01(4)	0.07(3)	-0.03(3)	0.00	-0.03(3)	-0.06(3)	-0.01(3)	0.00	-0.02(4)	-0.07(3)
C(5)	0.00	0.00	0.06(3)	0.00	-0.05(3)	0.45(4)	-0.02(4)	0.09(3)	-0.06(3)	-0.04(3)	-0.06(4)	0.01(4)	-0.11(4)	-0.06(4)	-0.07(5)	0.00
C(6)	0.02(3)	0.06(3)	0.05(3)	0.01(2)	0.36(3)	-0.01(3)	0.00	-0.08(3)	-0.02(3)	-0.04(3)	0.03(3)	-0.09(3)	-0.10(3)	0.00	0.04(3)	-0.03(3)
C(7)	-0.02(3)	0.00	0.04(2)	0.02(3)	0.47(3)	0.02(3)	0.02(3)	-0.21(3)	-0.06(3)	-0.01(3)	-0.09(3)	0.03(3)	-0.06(3)	-0.04(3)	-0.03(3)	0.02(3)
C(8)	0.03(3)	0.00	0.00	0.01(3)	0.56(3)	0.00	0.02(3)	-0.24(4)	-0.09(3)	-0.01(3)	0.05(3)	-0.02(3)	0.08(3)	-0.03(3)	-0.14(3)	-0.05(3)
C(9)	0.01(2)	-0.07(3)	-0.01(3)	0.01(3)	0.46(3)	-0.11(3)	0.02(2)	-0.12(4)	0.00	-0.07(3)	-0.02(3)	0.00	0.00	0.02(3)	-0.16(3)	0.00
C(10)	-0.01(3)	0.00	0.01(3)	0.00	0.00	0.39(4)	-0.01(3)	-0.04(3)	-0.08(3)	0.08(3)	0.07(4)	-0.03(4)	0.04(4)	-0.05(4)	-0.07(4)	0.02(3)
C(11)	0.09(3)	0.08(2)	-0.03(2)	-0.06(2)	0.44(3)	-0.03(2)	0.00	-0.06(4)	0.11(3)	0.00	0.01(3)	0.00	0.02(3)	-0.06(3)	-0.10(3)	-0.07(3)
C(12)	0.09(3)	0.07(2)	0.04(3)	0.02(2)	0.45(3)	-0.01(3)	0.00	-0.14(3)	0.07(3)	0.00	0.00	0.00	-0.02(3)	0.01(3)	-0.06(3)	0.00
C(13)	0.00	-0.01(3)	-0.01(3)	0.03(3)	0.47(3)	-0.03(3)	-0.02(3)	-0.13(4)	-0.01(4)	-0.03(4)	0.12(4)	0.00	0.04(4)	0.03(4)	-0.12(4)	0.07(4)
C(14)	-0.01(3)	0.00	0.00	- 0.02(3)	0..55(3)	0.00	0.00	-0.24(4)	0.09(3)	-0.02(3)	-0.05(3)	0.01(4)	-0.04(3)	-0.04(4)	-0.15(3)	0.03(3)
C(15)	-0.02(3)	-0.04(3)	-0.09(2)	0.00	0.48(3)	0.01(2)	0.03(3)	-0.18(3)	-0.07(3)	-0.02(3)	-0.10(3)	-0.11(3)	0.03(3)	-0.06(3)	0.00	0.00
C(16)	0.00	-0.04 (3)	0.00	0.07(3)	0.69(3)	-0.01(2)	0.00	-0.25(4)	0.04(3)	-0.06(3)	0.05(3)	0.00	0.02(3)	0.00	-0.21(3)	0.00
C(17)	-0.02(3)	0.00	0.04(3)	0.13(3)	0.57(3)	0.06 (3)	-0.08(3)	-0.22(4)	0.02(3)	0.04(3)	-0.03(3)	-0.09(3)	0.01(3)	-0.09(3)	-0.13(3)	0.08(3)
C(18)	0.00	-0.06(2)	-0.05(3)	0.01(2)	0.36(3)	0.02(3)	-0.04(3)	-0.06(3)	0.00	0.00	0.04(3)	0.02(3)	0.00	0.04(3)	-0.06(3)	-0.03(3)

Appendix G.

Electron density study of 17α-estradiol

17α-ESTRADIOL

Data collection, Processing, conventional and multipole refinement Details.

Unit Cell parameters

a=7.1176(9)Å b=23.2881(29)Å c=9.0614(11)Å β=98.985(3)°

$P2_1$ Z=4

Radiation used: Mo

Data processing

Saint integration

Sadabs 2.03 Ver.

Sortav scaling and averaging

Scaling

I	SCALEK(I)	SIGMAK(I)	R(I)	Z(I)	NDATA(I)
1	1.00000	0.00000	0.0389	1.018	4701
2	1.00994	0.00086	0.0389	1.034	4720
3	1.02345	0.00088	0.0386	1.026	4673
4	1.03665	0.00087	0.0387	1.028	4717
5	1.03349	0.00086	0.0384	1.032	4706
6	1.02760	0.00089	0.0386	1.027	4733
7	1.01383	0.00089	0.0376	1.021	4716
8	1.00551	0.00086	0.0379	1.015	4731
9	1.01740	0.00093	0.0452	0.899	7780
10	1.02698	0.00097	0.0423	0.856	7541
11	1.03336	0.00096	0.0468	0.947	7198
12	1.01940	0.00097	0.0359	0.927	4915
13	1.01988	0.00093	0.0421	0.900	7764
14	1.03243	0.00091	0.0395	0.852	7635
15	1.01698	0.00138	0.0598	0.939	4088

99238 TOTAL MEASUREMENTS

2 MEASUREMENTS REJECTED AS ABNORMAL OULIERS

99236 MEASUREMENTS ACCEPTED

3164 UNIQUE DATA MEASURED ONLY ONCE

3626 UNIQUE DATA MEASURED TWICE

14692 UNIQUE DATA MEASURED THREE OR MORE TIMES

21482 UNIQUE DATA

	NTERMS	NMEANS	<N>	R1	R2	RW	Z
ALL DATA	96072	18318	5.2	0.0288	0.0233	0.0863	1.083
Q > 0	96008	18294	5.2	0.0288	0.0233	0.0862	1.083
Q > 1	94579	17943	5.3	0.0285	0.0233	0.0835	1.070
Q > 2	91107	17017	5.4	0.0280	0.0233	0.0775	1.041
Q > 3	86715	15890	5.5	0.0274	0.0232	0.0712	1.015
Q > 4	82101	14781	5.6	0.0268	0.0232	0.0653	0.993
Q > 6	73564	12735	5.8	0.0257	0.0232	0.0559	0.955

BIVARIATE ANALYSIS OF VARIANCE

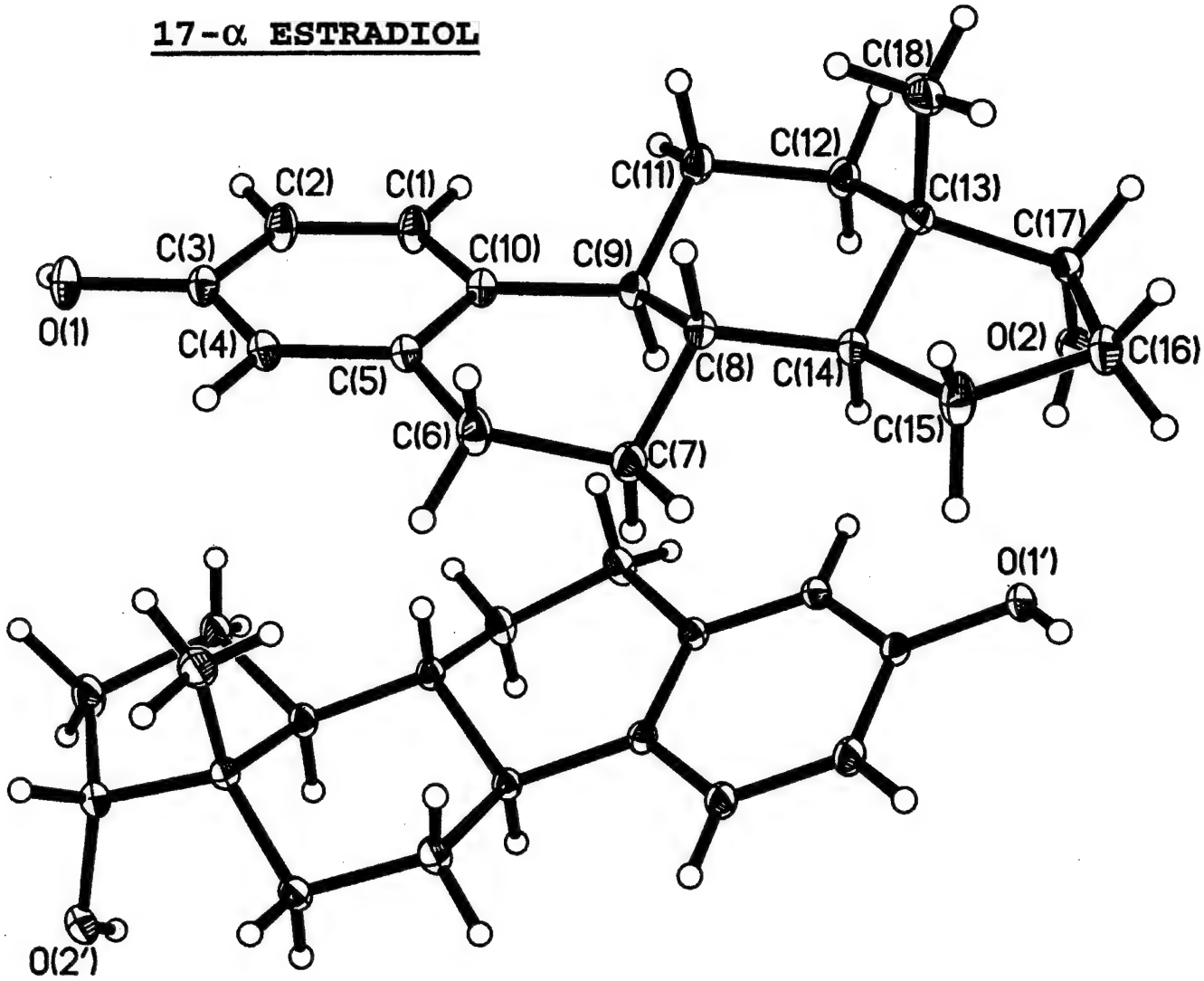
<Q>, Q = RMSD(Y)/ESD(Y)
<E>, E = ESD(Y)
<Y>, Y = F OR F^2
<S>, S = SIN(THETA)/LAMBDA
N, N = NUMBER OF UNIQUE DATA

0.93	0.90	0.90	0.92	0.81	0.83	0.88	0.92	0.98	1.03
0.317E+01	0.162E+01	0.133E+01	0.130E+01	0.109E+01	0.986E+00	0.972E+00	0.871E+00	0.809E+00	0.796E+00
0.163E+03	0.408E+02	0.220E+02	0.206E+02	0.167E+02	0.119E+02	0.108E+02	0.754E+01	0.572E+01	0.514E+01
0.332	0.504	0.599	0.671	0.732	0.785	0.833	0.877	0.918	0.941
2147	2149	2147	2105	1983	1931	1893	1843	1815	305

SHELX-refinement

R1 = 0.0496 for 19870 Fo > 4sig(Fo) and 0.0550 for all 21482 data
wR2 = 0.1092, GooF =1.167,

17-α ESTRADIOL



MODEL 1

(Kappa values K_{CH} & K_{OH}= 1.2)

XD-refinement

Resolution Used $(\sin\theta/\lambda)_{max}=1.059\text{Å}^{-1}$

R(F) = 0.0347	Rall(F) = 0.0460	Rw(F) = 0.0336
$R(F^2)$ = 0.0384	Rall(F^2) = 0.0414	Rw(F^2)= 0.0601
GOFw = 1.1113	GOF = 1.1113	Nref/Nv=18.5587

Refined First Kappa values

		κ	κ'(fixed)
O1, O2		0.983	1.16
C3		1.002	0.92
C16,C17		1.004	0.95
C1,C2,C4		0.980	0.92
C5,C10		0.974	0.87
C6,C7,C8,C9,C11, C12,C13,C14,C15		0.986	0.95
H-atoms	OH:	1.2	0.29
	CH:	1.2	0.29

Differences of Mean-Squares Displacement Amplitudes (DMSDA) (1.E4 A2) along interatomic vectors (*bonds)**

ATOM-->	ATOM	/	DIST	DMSDA	ATOM	/	DIST	DMSDA	ATOM	/	DIST	DMSDA
Molecule 1												
O(1)	C(3)	*	1.3729	1								
O(2)	C(17)	*	1.4361	10								
C(1)	C(2)	*	1.3948	2	C(10)	*	1.4021	-1				
C(2)	C(3)	*	1.3966	1								
C(3)	C(4)	*	1.3883	-3								
C(4)	C(5)	*	1.3991	-5								
C(5)	C(6)	*	1.5107	10	C(10)	*	1.4066	0				
C(6)	C(7)	*	1.5258	7								
C(7)	C(8)	*	1.5270	-5								
C(8)	C(9)	*	1.5426	-4	C(14)	*	1.5263	-1				
C(9)	C(10)	*	1.5261	-6	C(11)	*	1.5416	3				
C(11)	C(12)	*	1.5392	-3								
C(12)	C(13)	*	1.5260	1								
C(13)	C(14)	*	1.5416	0	C(17)	*	1.5447	-3	C(18)	*	1.5381	19
C(14)	C(15)	*	1.5347	1								
C(15)	C(16)	*	1.5570	1								
C(16)	C(17)	*	1.5514	11								
Molecule 2												
O(1')	C(3')	*	1.3654	-12								
O(2')	C(17')	*	1.4332	9								
C(1')	C(2')	*	1.3926	9	C(10')	*	1.4010	-9				
C(2')	C(3')	*	1.3943	3								
C(3')	C(4')	*	1.3906	-11								
C(4')	C(5')	*	1.3960	2								
C(5')	C(6')	*	1.5130	7	C(10')	*	1.4074	-4				
C(6')	C(7')	*	1.5252	2								
C(7')	C(8')	*	1.5239	-1								
C(8')	C(9')	*	1.5436	2	C(14')	*	1.5232	-3				
C(9')	C(10')	*	1.5265	-1	C(11')	*	1.5378	6				
C(11')	C(12')	*	1.5384	-3								

```
C(8')    C(9')    * 1.5440     3 C(14')   * 1.5234    -2
C(9')    C(10')   * 1.5267     0 C(11')   * 1.5378     6
C(11')   C(12')   * 1.5384    -2
C(12')   C(13')   * 1.5265    -4
C(13')   C(14')   * 1.5405    -2 C(17')   * 1.5448     7 C(18')   * 1.5395     2
C(14')   C(15')   * 1.5297     1
C(15')   C(16')   * 1.5490     1
C(16')   C(17')   * 1.5517     6
-------------------------------------------------------------------------------
```

Monopole populations from the multipole refinement

Atom	Mol 1	Mol 2		Atom	Mol1	Mol2
O1	-0.33	-0.43		H1A	0.18	0.20
O2	-0.46	-0.42		H2A	0.16	0.22
C1	-0.19	-0.23		H1	0.29	0.29
C2	-0.28	-0.33		H2	0.21	0.20
C3	0.15	0.10		H4	0.21	0.19
C4	-0.25	-0.27		H6A=H6B	0.20	0.23
C5	-0.13	-0.13		H7A=H7B	0.22	0.23
C6	-0.29	-0.25		H8	0.19	0.23
C7	-0.32	-0.26		H9	0.20	0.18
C8	-0.19	-0.17		H11A=H11B	0.20	0.20
C9	-0.16	-0.14		H12A=H12B	0.22	0.23
C10	-0.09	-0.17		H14	0.21	0.19
C11	-0.30	-0.32		H15A=H15B	0.20	0.18
C12	-0.34	-0.31		H16A=H16B	0.19	0.14
C13	-0.21	-0.28		H17	0.12	0.13
C14	-0.24	-0.16		H18A=H18B=H18C	0.13	0.19
C15	-0.33	-0.35				
C16	-0.35	-0.39				
C17	0.17	0.16				
C18	-0.48	-0.43				

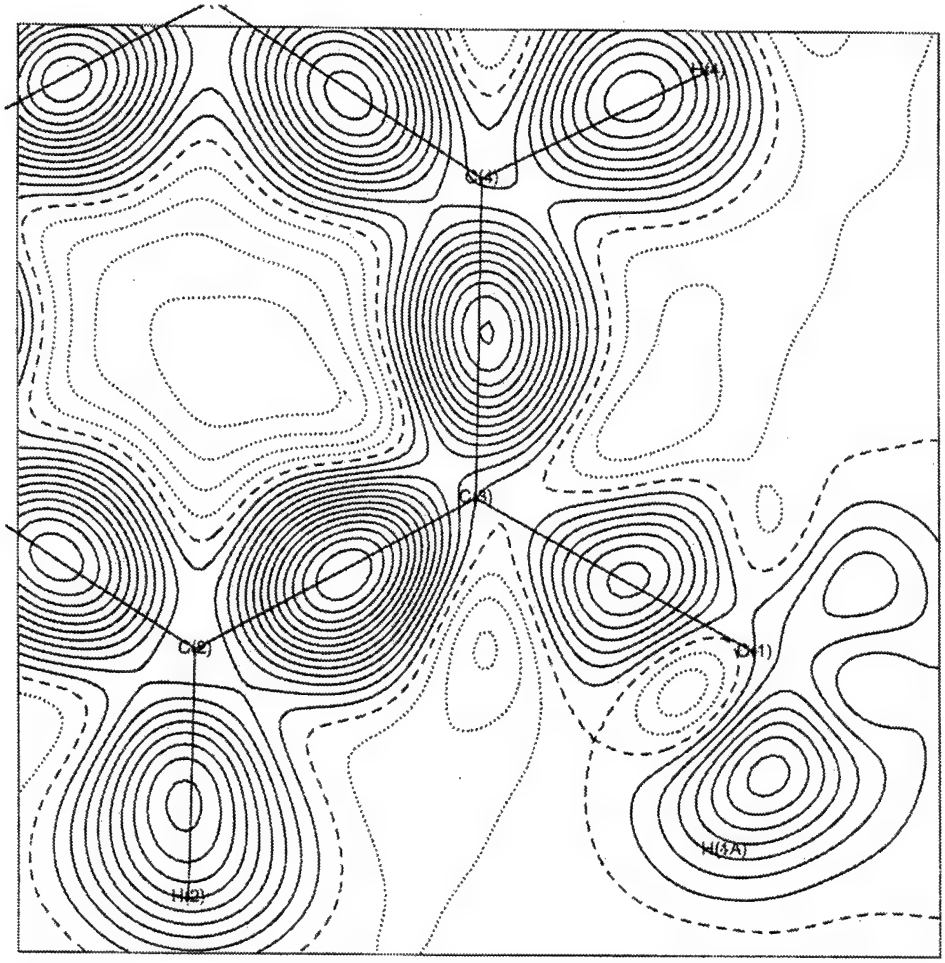


Figure 1. Model multipole deformation electron density in the aromatic ring plane. Contour interval is 0.05 eA^{-3}.

Bond critical points in α- estradiol

Bond	ρ	$\nabla^2\rho$	ε		ρ	$\nabla^2\rho$	ε
C3-O1	2.10	-21.9	0.12	------	2.32	-23.3	0.10
C17-O2	1.85	-12.6	0.11		1.97	-11.7	0.06
A-ring							-
C1-C2	2.23	-22.4	0.32		2.30	-23.4	0.19
C2-C3	2.32	-25.6	0.29		2.28	-23.4	0.31
C3-C4	2.24	-24.2	0.35		2.34	-26.2	0.22
C5-C10	2.20	-22.6	0.34		2.23	-23.7	0.32
C1-C10	2.21	-23.3	0.33		2.24	-23.5	0.20
B-ring							
C5-C6	1.82	-14.2	0.07		1.75	-12.8	0.22
C6-C7	1.69	-11.2	0.12		1.73	-13.2	0.03
C7-C8	1.65	-11.6	0.10		1.73	-13.6	0.04
C8-C9	1.62	-12.4	0.06		1.63	-11.1	0.04
C9-C10	1.76	-14.9	0.14		1.69	-12.5	0.16
C & D-ring							
C9-C11	1.64	-11.0	0.13		1.67	-11.8	0.12
C11-C12	1.67	-11.5	0.03		1.67	-10.8	0.08
C12-C13	1.70	-12.1	0.09		1.80	-12.2	0.03
C13-C14	1.63	-11.2	0.03		1.70	-11.4	0.06
C14-C15	1.66	-10.7	0.05		1.65	-10.5	0.07
C15-C16	1.52	-9.6	0.13		1.64	-10.4	0.09
C16-C17	1.57	-9.1	0.06		1.66	-11.1	0.01
C17-C13	1.69	-11.9	0.15		1.60	-10.4	0.02
C13-C18	1.75	-10.4	0.09		1.81	13.1	0.06
	ρ	$\nabla^2\rho$	ε		ρ	$\nabla^2\rho$	ε
O1-H1A	2.45	-32.8	0.01	------	2.41	-34.3	0.03
O2-H2A	2.65	-37.5	0.04		2.76	-47.6	0.04
C1-H1	1.86	-21.0	0.10		1.84	-18.8	0.08
C2-H2	1.87	-18.0	0.09		1.88	-18.6	0.09
C4-H4	1.88	-19.6	0.12		1.90	-19.6	0.11
C6-H6A	1.80	-16.2	0.06		1.84	-17.6	0.08
C6-H6B	1.74	-13.8	0.07		1.77	-16.2	0.06
C7-H7A	1.82	-16.9	0.02		1.89	-18.0	0.06
C7-H7B	1.74	-14.9	0.11		1.76	-16.3	0.07
C8-H8	1.78	-13.2	0.04		1.77	-17.0	0.01
C9-H9	1.81	-15.6	0.01		1.83	-16.0	0.02
C11-H11A	1.73	-14.3	0.05		1.80	-15.0	0.02
C11-H11B	1.78	-14.7	0.08		1.89	-17.7	0.06
C12-H12A	1.74	-14.9	0.04		1.87	-18.0	0.02
C12-H12B	1.81	-12.2	0.06		1.82	-17.3	0.03
C14-H14	1,87	-18.2	0.06		1.83	-16.4	0.03
C15-H15A	1.70	-14.3	0.05		1.82	-15.9	0.10
C15-H15B	1.76	-15.2	0.08		1.74	-14.7	0.08
C16-H16A	1.88	-18.2	0.06		1.79	-14.8	0.19
C16-H16B	1.85	-17.6	0.03		1.83	-16.3	0.14
C17-H17	1.91	-18.5	0.04		1.80	-16.7	0.03
C18-H18A	1.82	-12.3	0.14		1.95	-19.3	0.03
C18-H18B	1.63	-8.8	0.15		1.85	-16.5	0.15
C18-H18C	1.81	-13.7	0.14		1.93	-18.5	0.10

MODEL 2

(Kappa values K_{CH} =1.4, K_{OH}=1.3)

Xd-refinement

Resolution Used $(\sin\theta/\lambda)_{max}$=1.059Å^{-1}

R{ F } = 0.0350	Rall{ F } = 0.0464	Rw{ F } =	0.0337
R{ F^2} = 0.0397	Rall{F^2} = 0.0426	Rw{ F^2} =	0.0604
GOFw = 1.1160	GOF = 1.1160	Nref/Nv =	18.5587

Refined first Kappa values

		κ	κ' (fixed)
O1, O2		0.984	1.16
C3		1.001	0.92
C16,C17		1.008	0.95
C1,C2,C4		0.974	0.92
C5,C10		0.975	0.87
C6,C7,C8,C9,C11, C12,C13,C14,C15		0.984	0.95
H-atoms	OH:	1.3	0.29
	CH:	1.4	0.29

Differences of Mean-Squares Displacement Amplitudes (DMSDA)
(1.E4 A**2) along interatomic vectors (*bonds)

ATOM-->	ATOM	/	DIST	DMSDA	ATOM	/	DIST	DMSDA	ATOM	/	DIST	DMSDA
Molecule 1												
O(1)	C(3)	*	1.3728	4								
O(2)	C(17)	*	1.4361	12								
C(1)	C(2)	*	1.3948	2	C(10)	*	1.4023	-1				
C(2)	C(3)	*	1.3966	2								
C(3)	C(4)	*	1.3883	-3								
C(4)	C(5)	*	1.3990	-5								
C(5)	C(6)	*	1.5108	8	C(10)	*	1.4068	0				
C(6)	C(7)	*	1.5259	7								
C(7)	C(8)	*	1.5272	-5								
C(8)	C(9)	*	1.5428	-4	C(14)	*	1.5264	-1				
C(9)	C(10)	*	1.5261	-6	C(11)		1.5420	3				
C(11)	C(12)	*	1.5393	-3								
C(12)	C(13)	*	1.5260	1								
C(13)	C(14)	*	1.5417	0	C(17)	*	1.5447	-3	C(18)	*	1.5382	19
C(14)	C(15)	*	1.5347	1								
C(15)	C(16)	*	1.5570	1								
C(16)	C(17)	*	1.5512	12								
Molecule 2												
O(1')	C(3')	*	1.3655	-10								
O(2')	C(17')	*	1.4332	10								
C(1')	C(2')	*	1.3927	8	C(10')	*	1.4011	-8				
C(2')	C(3')	*	1.3943	3								
C(3')	C(4')	*	1.3906	-9								
C(4')	C(5')	*	1.3960	2								
C(5')	C(6')	*	1.5131	6	C(10')	*	1.4076	-3				
C(6')	C(7')	*	1.5254	3								
C(7')	C(8')	*	1.5242	-1								

```
C(12')   C(13')  * 1.5266    -4
C(13')   C(14')  * 1.5401    -3 C(17')  * 1.5447     8 C(18')  * 1.5396     3
C(14')   C(15')  * 1.5295     2
C(15')   C(16')  * 1.5490     2
C(16')   C(17')  * 1.5514     4
--------------------------------------------------------------------------------
```

Monopole populations from the multipole refinement

Atom	Mol 1	Mol 2		Atom	Mol1	Mol2
O1	-0.29	-0.41		H1A	0.18	0.19
O2	-0.44	-0.38		H2A	0.11	0.15
C1	-0.13	-0.18		H1	0.27	0.27
C2	-0.19	-0.24		H2	0.16	0.17
C3	0.19	0.12		H4	0.19	0.16
C4	-0.13	-0.20		H6A=H6B	0.15	0.19
C5	-0.12	-0.12		H7A=H7B	0.18	0.18
C6	-0.23	-0.19		H8	0.16	0.21
C7	-0.27	-0.21		H9	0.16	0.15
C8	-0.15	-0.11		H11A=H11B	0.14	0.14
C9	-0.12	-0.10		H12A=H12B	0.17	0.18
C10	-0.09	-0.16		H14	0.19	0.17
C11	-0.24	-0.29		H15A=H15B	0.17	0.15
C12	-0.28	-0.28		H16A=H16B	0.16	0.10
C13	-0.16	-0.24		H17	0.10	0.12
C14	-0.20	-0.11		H18A=H18B=H18C	0.07	0.14
C15	-0.26	-0.26				
C16	-0.28	-0.30				
C17	0.17	0.18				
C18	-0.44	-0.41				

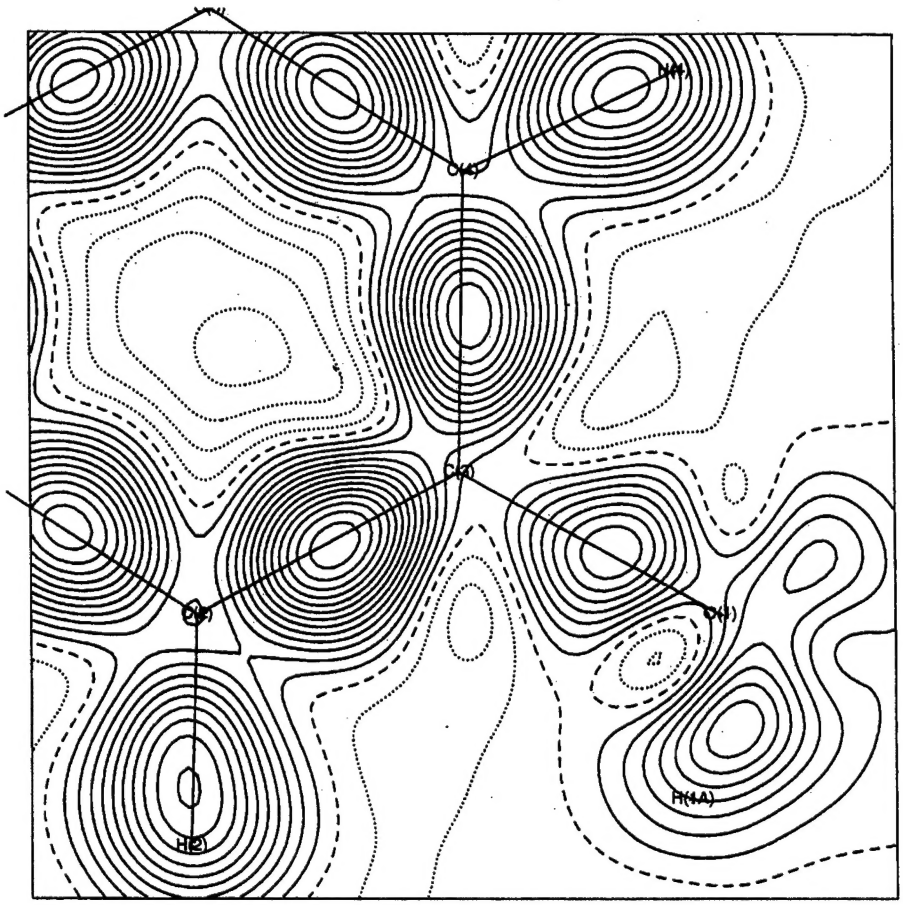


Figure 2. Model multipole deformation electron density in the aromatic ring plane. Contour interval is 0.05 eA^{-3}.

U_{iso} for the hydrogen atoms

Atom	Mol1	Mol2
H1A	0.048	0.048
H2A	0.050	0.047
H1	0.042	0.043
H2	0.050	0.050
H4	0.047	0.048
H6A	0.052	0.054
H6B	0.049	0.045
H7A	0.042	0.047
H7B	0.053	0.045
H8	0.038	0.041
H9	0.041	0.045
H11A	0.057	0.044
H11B	0.045	0.035
H12A	0.041	0.037
H12B	0.051	0.044
H14	0.046	0.043
H15A	0.051	0.060
H15B	0.055	0.049
H16A	0.047	0.055
H16B	0.050	0.067
H17	0.043	0.046
H18A	0.064	0.046
H18B	0.061	0.051
H18C	0.050	0.053

Multipole populations

Atom	Mol 1			Mol 2			Atom	Mol1	Mol2
	20	33+	32-	20	33+	32-		D10	D10
C1	-0.19	0.33		-0.29	0.32		H1A	0.18	0.14
C2	-0.22	0.33		-0.23	0.31		H2A	0.17	0.24
C3	-0.15	0.38		-0.19	0.36		H1	0.21	0.13
C4	-0.19	0.33		-0.25	0.33		H2	0.09	0.15
C5	-0.25	0.36		-0.19	0.39		H4	0.15	0.18
C6			0.33			0.35	H6A=H6B	0.12	0.16
C7			0.34			0.35	H7A=H7B	0.12	0.13
C8			0.39			0.41	H8	0.02	0.12
C9			0.43			0.35	H9	0.06	0.14
C10	-0.24	0.43		-0.24	0.40		H11A=H11B	0.11	0.11
C11			0.29			0.36	H12A=H12B	0.07	0.18
C12			0.34			0.32	H14	0.16	0.15
C13			0.41			0.26	H15A=H15B	0.08	0.13
C14			0.36			0.32	H16A-H16B	0.14	0.18
C15			0.31			0.18	H17	0.17	0.16
C16			0.36			0.30	H18A=B=C	0.07	0.17
C17			0.31			0.29			
C18			0.13			0.24			

Bond critical points in α- estradiol

Bond	ρ	$\nabla^2\rho$	ε		ρ	$\nabla^2\rho$	ε
C3-O1	2.10	-20.3	0.12	------	2.27	-22.6	0.10
C17-O2	1.82	-11.7	0.12		1.94	-10.4	0.10
A-ring							
C1-C2	2.22	-22.1	0.29		2.28	-23.0	0.19
C2-C3	2.32	-24.7	0.27		2.26	-22.5	0.29
C3-C4	2.23	-23.3	0.32		2.33	-24.8	0.20
C5-C10	2.20	-22.0	0.32		2.19	-22.0	0.31
C1-C10	2.20	-22.6	0.30		2.22	-22.5	0.20
B-ring							
C5-C6	1.81	-13.9	0.09		1.75	-13.1	0.21
C6-C7	1.70	-11.4	0.09		1.71	-12.4	0.05
C7-C8	1.64	-10.7	0.08		1.72	-12.7	0.02
C8-C9	1.62	-11.8	0.04		1.63	-10.5	0.04
C9-C10	1.77	-14.2	0.14		1.69	-12.1	0.14
C & D-ring							
C9-C11	1.63	-10.4	0.12		1.66	-11.2	0.11
C11-C12	1.66	-11.1	0.03		1.64	-10.2	0.08
C12-C13	1.68	-11.5	0.10		1.76	-11.4	0.03
C13-C14	1.62	-10.6	0.03		1.69	-10.6	0.07
C14-C15	1.65	-10.0	0.04		1.67	-10.3	0.07
C15-C16	1.49	-8.7	0.16		1.64	-9.9	0.06
C16-C17	1.55	-8.2	0.05		1.64	-10.0	0.01
C17-C13	1.67	-10.9	0.17		1.62	-9.8	0.01
C13-C18	1.73	-10.1	0.06		1.78	12.4	0.06
	ρ	$\nabla^2\rho$	ε		ρ	$\nabla^2\rho$	ε
O1-H1A	2.61	-23.7	0.02	------	2.59	-27.3	0.03
O2-H2A	2.74	-28.9	0.04		2.78	-38.5	0.04
C1-H1	1.93	-20.1	0.11		1.97	-17.9	0.08
C2-H2	1.92	-16.0	0.10		1.93	-17.1	0.10
C4-H4	1.94	-17.7	0.13		1.97	-18.9	0.10
C6-H6A	1.86	-14.6	0.07		1.91	-16.2	0.11
C6-H6B	1.79	-12.4	0.10		1.84	-14.7	0.06
C7-H7A	1.87	-15.1	0.01		1.92	-15.4	0.08
C7-H7B	1.81	-13.2	0.12		1.80	-14.2	0.09
C8-H8	1.86	-11.4	0.05		1.87	-16.3	0.02
C9-H9	1.87	-14.3	0.01		1.92	-15.4	0.01
C11-H11A	1.78	-12.5	0.05		1.82	-13.2	0.03
C11-H11B	1.82	-12.5	0.10		1.93	-15.8	0.08
C12-H12A	1.80	-12.4	0.05		1.93	-16.7	0.02
C12-H12B	1.79	-12.3	0.07		1.90	-16.5	0.04
C14-H14	1.97	-17.3	0.07		1.93	-15.5	0.05
C15-H15A	1.74	-11.6	0.08		1.87	-13.6	0.11
C15-H15B	1.80	-12.5	0.11		1.80	-13.1	0.08
C16-H16A	1.90	-15.5	0.09		1.84	-13.1	0.20
C16-H16B	1.89	-15.5	0.06		1.88	-14.6	0.15
C17-H17	1.94	-16.2	0.06		1.85	-14.4	0.03
C18-H18A	1.83	-8.9	0.19		1.95	-16.5	0.03
C18-H18B	1.68	-7.5	0.16		1.90	-14.8	0.19
C18-H18C	1.81	-10.9	0.15		1.95	-16.4	0.05